Consultation Draft Report of the Drug Resistance Working Group

COMMENTS WELCOME
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About the Drug Resistance Working Group

The Center for Global Development's Drug Resistance Working Group (DRWG) was convened in Fall 2007 to identify practical and feasible ways that donors, multilateral organizations, NGOs, and other actors at the global level could prevent or contain the emergence of drug resistance affecting high-burden diseases in developing countries through improvements in common-property management, information flows, and R&D investments. Given the depth and breadth of the issue, and the myriad interrelated factors that play a role in drug resistance, working group membership needed to be equally as comprehensive to adequately address the problem. To ensure that all perspectives were given an equal voice, membership consisted of experts from all relevant sectors and backgrounds. While all members participated in a personal capacity on a voluntary basis, the group included health economists, medical doctors, pharmacists, microbiologists, public health practitioners, global health policy experts, lawyers, and business executives from academia, industry, government (both donor and recipient), non-profits, multilateral organizations, NGOs, and foundations. Equally as important, we also strived to have members from developing countries, in order to always stay firmly grounded in the realities faced by resource poor nations and health systems. (Please see the annex for a full list of working group members and bios.)

This consultation draft is drawn from analyses, discussions and other inputs from the Drug Resistance Working Group. However, the views expressed in this report are those of the authors and do not necessarily reflect the views of working group members, the Center for Global Development, or its funders. After input from this consultation process, a final consensus report will be issued by the working group.

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Glossary of Terms and Acronyms

Acquired Resistance – as defined by the *Disease Control Priorities Project, "de novo* or acquired resistance results in the appearance of a resistant strain in a single patient."

ACTs – artemisinin-based combination therapies: the WHO-recommended malaria treatment in high-burden areas

ADDOs – accredited drug dispensing outlets

AIDS – Acquired Immune Deficiency Syndrome

AMR – antimicrobial resistance = general term used to describe all drug resistance

Antimicrobial Resistance – Ability of a parasite [microbe] strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject. (WHO, 1973)

APUA – Alliance for the Prudent Use of Antibiotics

ARI – acute respiratory infection

ART – anti-retroviral therapy = standard treatment for HIV/AIDS patients, it consists of multiple anti-retroviral drugs given in combination

ARVs – anti-retroviral (drugs)

CDC – U.S. Center for Disease Control and Prevention

CDD – Collaborative Drug Discovery

CPE/CPD – continuing professional education/development

CQ – chloroquine: an antimalarial drug

DDW – diseases of the developing world

DNDi – Drugs for Neglected Diseases initiative

DOTS – directly observed therapy, short course = standard tuberculosis treatment recommended by the World Health Organization

DRWG – Drug Resistance Working Group, of the Center for Global Development

DSTs – drug susceptibility tests

EADSI – East African Drug Seller Initiative

EANMAT – East African Network for Monitoring Anti-Malarial Treatment

ECOWAS – Economic Community of West African States

EMEA – European Medicines Agency

FDCs – fixed-dose combination (drugs)

FIND – Foundation for Innovative New Diagnostics

FIP – International Pharmaceutical Federation

GMP – good manufacturing processes

GSK – GlaxoSmithKline

HIV – Human Immunodeficiency Virus

HIV ResNet – Global HIV Drug Resistance Surveillance Network, of the World Health Organization

ICH – International Conference on Harmonization

ICIUM – International Conference on Improving the Use of Medicines

IDRDC – International Drug Resistance and Development Conference

IHR – International Health Regulations

INRUD – International Network for the Rational Use of Drugs

InSTEDD – Innovative Support to Emergencies Diseases and Disasters

ISO – International Organization for Standardization

IT – information technology

IUATLD – International Union against Tuberculosis and Lung Disease

MDR-TB – multi-drug resistant tuberculosis = A strain of M. Tuberculosis resistant to both first-line treatments rifampicin and isoniazid.

MoH – Ministry of Health

MSH – Management Sciences for Health

MRSA – methicillin-resistant Staphylococcus aureus

NDRAs – national drug regulatory agencies

NGO – non-governmental organization

NIH – U.S. National Institutes of Health

OSDD – Open Source Drug Discovery

PDP – product development partnership

POC – point-of-care (diagnostics)

Primary Resistance – "Subsequent transmission of such resistant strains from an infectious case to other persons leads to disease that is drug resistant from the outset, a phenomenon known as primary resistance."

R&D – research and development

SIDA – Swedish International Development Agency

SP – sulfadoxine-pyrimethamine: a combination therapy for malaria treatment

SRLN – Supranational Laboratory Network (for TB), of the WHO/IUATLD

STGs – standard treatment guidelines

TA – technical assistance

TB - tuberculosis

TFDA – Tanzanian Food and Drug Authority

USAID – U.S. Agency for International Development

USP – United States Pharmacopeia

WADRAN – West African Drug Regulatory Authority Network

WATCH - Worldwide Analysis of Resistance Transmission over Time of Chronically and Acute Infected HIV-1 infected persons

WHO – World Health Organization

WHO/TDR – WHO's Special Programme for Research and Training in Tropical Diseases

WWARN – Worldwide Antimalarial Resistance Network

XDR-TB – extensively drug-resistance tuberculosis = A strain of M. Tuberculosis resistant to both first-line treatments rifampicin and isoniazid, any member of the quinolone family and at least one of the second-line anti-TB injectible drugs: kanamycin, capreomycin, or amikacin.

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In an increasingly interconnected world, the problems posed by drug resistance have moved from the patient's bedside to threaten global public health. Drug resistance has dramatically increased the costs of fighting TB and malaria, reversed or slowed gains against childhood diarrhea and pneumonia, and threatens to undermine the strong push to effectively treat persons living with HIV/AIDS. Weak or non-existent prevention and management of infectious disease in many community settings, ill-informed and inappropriate drug choices by dispensers and prescribers, and harmful drug-taking behaviors by patients occur everywhere. These conditions create the petri dish out of which drug resistance emerges and then spreads as quickly as people move around the globe.

Drug resistance will not be solved at the patient's bedside, although effective infection control in clinical settings is an essential life-saving step. Drug resistance is present in communities around the world. It is result of normal evolutionary processes in response to treatment for all major infectious diseases, but it is increasingly subverting efforts to improve the health of the world's poor, especially children. We cannot afford to be indifferent to its spread. We do not and will not for the foreseeable future have enough effective drugs to treat resistant forms of diseases if they become the norm. New solutions, scaling up solutions that work, and showing far greater leadership are all urgently needed if we are to make headway against infectious diseases.

The Center for Global Development's Drug Resistance Working Group[*] was convened in late 2007 to identify practical and feasible ways for donors, multilateral organizations, non-governmental organizations (NGOs), and private companies to prevent or contain the emergence of resistance to drugs for high-burden diseases affecting developing countries.

[*] See Appendix A and www.cgdev.org/Drug_Resistance to learn more about the objectives, process and members of the Drug Resistance Working Group

Following a review of many valiant but failed efforts to stall the relentless spread of drug-resistant pathogens, the CGD working group adopted an ambitious scope of work guided by some key understanding and principles:

- The ability of the world's drug supply to cure people is rapidly eroding and needs protection.
- Resistance to antibiotics, antivirals, and antimalarials has many common drivers.
- Actions are required at the global level as well as national and local levels.
- Efforts to increase access to drugs should explicitly embrace safety, efficacy, and sustainability.

The working group members brought to the drug resistance problem scientific expertise in multiple infectious diseases, drugs and diagnostics research and development, clinical experience in different settings, and program and policy knowledge. They identified knowledge gaps and commitment gaps that are jointly responsible for the precariousness of the world's ability to treat disease. The working group commissioned new research to fill critical knowledge gaps in four areas:

- Review of global resistance patterns affecting all major infectious diseases
- Drug resistance information and information-sharing
- Weaknesses in drug development and delivery supply chain related to resistance
- Link between animal and human use of antibiotics

The working group drew from those research efforts (available in full here) and a wide range of other sources to develop a set of interlocking recommendations that comprise a comprehensive, coherent, and ambitious plan for tackling drug resistance. The plan includes steps that individually could go far to improve treatment of life-threatening diseases around the world, but collectively create both the foundation and the layers of actions necessary to assure each and every sick individual that the cure available to them is a cure that will work.

I. Introduction

Deadly diseases are becoming resistant to drugs faster than we can develop new treatments. Drug resistance quickly transforms infections that can be managed easily into life-threatening ones. It undermines health care around the world, vastly increasing costs in dollars and lives. Tackling resistance effectively is complicated by enormous gaps in our knowledge about where resistance lurks and how it is spreading. And while international funders and developing country governments rightly invest in increasing access to drugs in developing countries—to the point where the purchase of drugs accounts for well over half of development assistance for health—they do far less to protect and preserve the efficacy of those drugs. In some instances, the practices of those who are seeking to expand access can unintentionally accelerate the spread of resistance. Understanding how to slow the emergence of drug resistance constitutes a vital, yet much underappreciated, dimension of fulfilling the global commitment to ensure access to quality pharmaceutical products.

The Center for Global Development's Drug Resistance Working Group[*] was convened in late 2007 to identify practical and feasible ways for donors, multilateral organizations, non-governmental organizations (NGOs), and private companies to prevent or contain the emergence of resistance to drugs for high-burden diseases affecting developing countries. This report offers eight specific recommendations for action that these groups can take to prevent and contain drug resistance.

Drug Resistance is Increasing Globally

Resistance is on the rise. An increasing number of pathogens are resistant to one or more drugs used to treat the diseases they cause. Indeed, many diseases common in developing

[*] See Appendix A and www.cgdev.org/Drug_Resistance to learn more about the objectives, process and members of the Drug Resistance Working Group

countries—including malaria, streptococcus pneumonia, cholera, and shigella—are now resistant to multiple drugs. This is true for diseases that afflict rich countries as well as poor ones, such as tuberculosis (TB) and many other bacterial infections. Drug-resistant TB is spreading rapidly to countries where it has not been seen before.[1] Resistance, or decreased sensitivity of disease-causing organisms to drugs that used to be very effective, has been observed for *all* currently available antimalarials, including artimesinin-containing products that have only recently been introduced. Countries have repeatedly changed their standard treatment guidelines for malaria because of unacceptable levels of resistance to the drugs in use.[*] Still more worrisome is that resistance to one type of drug for one disease doesn't stop there. Many diseases share the same drug treatments; antibiotics, especially, are needed to treat the major childhood respiratory and diarrheal diseases, but are also essential to the treatment of TB and HIV/AIDS. Further, increasingly numbers of people are co-infected with more than one disease, notably TB and HIV/AIDS.[2]

Figure 1 on page 6 is a composite snapshot of available drug resistance data relating to selected infectious diseases across the world. No part of the map is "resistance-free." Importantly, the many blank spaces on the map reveal how extremely weak our current knowledge about drug resistance prevalence is.

The lack of information is a defining feature of drug resistance. Drug resistance moves invisibly through communities and clinics as microbes adapt to survive in the presence of drug therapy. Patients and their families often do not know why an illness has worsened, or become untreatable, particularly when they lack access to alternative therapies, professional monitoring of their condition, or drug-susceptibility tests. Health-information systems often do not record treatment failure, even when a patient dies because of it.

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[*] WHO "Susceptibility of Plasmodium Falciparum to Antimalarial Drugs Report (2004)" - http://www.who.int/malaria/rbm/Attachment/20041108/SusceptibilityPlasmodium_report.pdf

Take the example of TB: it is estimated that fewer than 1 in 20 cases of resistant TB are currently detected, and only 3 percent of known multi-drug-resistant TB (MDR-TB*) cases in high-burden countries are treated with newer, more expensive drugs.[3] Experts have pointed out that these figures merely "scratch the surface of our ignorance."[4] This means that hundreds of thousands of people are infected with drug-resistant TB but do not know it or cannot access treatment. Many other resistant infections go untreated, or are treated with ineffective drugs, only to be passed on in resistant form.

Drug resistance is not a new problem but it has been hastened by rapid increases in drug access and, all too often, inappropriate or suboptimal use across the world. In many ways, it is one of the costs of the tremendous success in expanding access to potent medicines. The number of people being treated for HIV/AIDS, for example, increased ten-fold between 2002 and 2007, there was an eight-fold rise in antimalarial treatment between 2005 and 2006, and the Stop TB Partnership's Global Drug Facility has expanded access to drugs for TB patients, offering nearly 14 million patient treatments in 93 countries since 2001.[5] While increased access to necessary drugs is clearly desirable, it brings challenges in preserving the efficacy of these drugs and ensuring they are used appropriately. ***It is absolutely vital that access to essential medicines continues to expand in developing countries to reach those in need, accompanied by specific measures to assure the safety, efficacy, and sustainability of those drugs for a larger group of patients.***

Too often, antibiotics are given for viral conditions and other health problems that cannot be treated with those drugs; or the wrong antibiotics are given; or the course of treatment is too short. Each of these is considered "inappropriate" drug use and exacerbates resistance. The WHO estimates that more than half of antibiotic use globally is inappropriate for one of these reasons.[6] The consequence is far less success in curing disease and saving lives than expected.

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* TB caused by *M. tuberculosis* strains resistant to at least two anti-TB drugs: isoniazid (INH) and rifampin (RIF).

DOCUMENTED EXAMPLES OF DRUG R

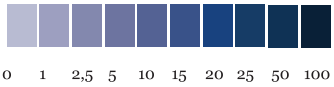
HIV

USA /United Kingdom

In New York, USA, primary resistance increased from 13.2% (1995-1998) to 24.1% (2003-2004) *1. In the UK, primary resistance for any ARV was reported to be 19.2% (2003) *2.

MDR-TB

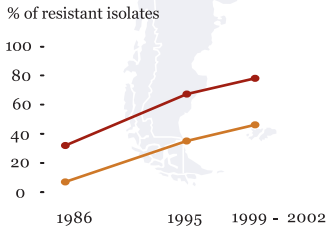
Number of cases of multi-drug resistant tuberculosis (in thousands) *6.



SHIGELLA

United States

Ampicillin-resistant *Shigella* ● strains increased from 32% in 1986, to 67% in 1995 to 78% of all isolates over the 1999-2002 period and while trimethoprim-sulfamethoxazole (TMP-SMX)-resistant *Shigella* ● strains increased from 7% in 1986, to 35% in 1995 to 46% over the 1999-2002 period *7.



Uganda

One study found that 100% of *Shigella* isolates were resistant to TMP-SMX, while only 33.4% were susceptible to ampicillin *8.

Note: Antibiotics commonly prescribed for Shigella include: Trimethoprim-sulfamethoxazole (TMP-SMX), tetracycline, chloramphenicol, nalidixic acid, ampicillin, ciprofloxacin, norfloxacin, ofloxacin, ceftriaxone, and

RESISTANCE BY DISEASE

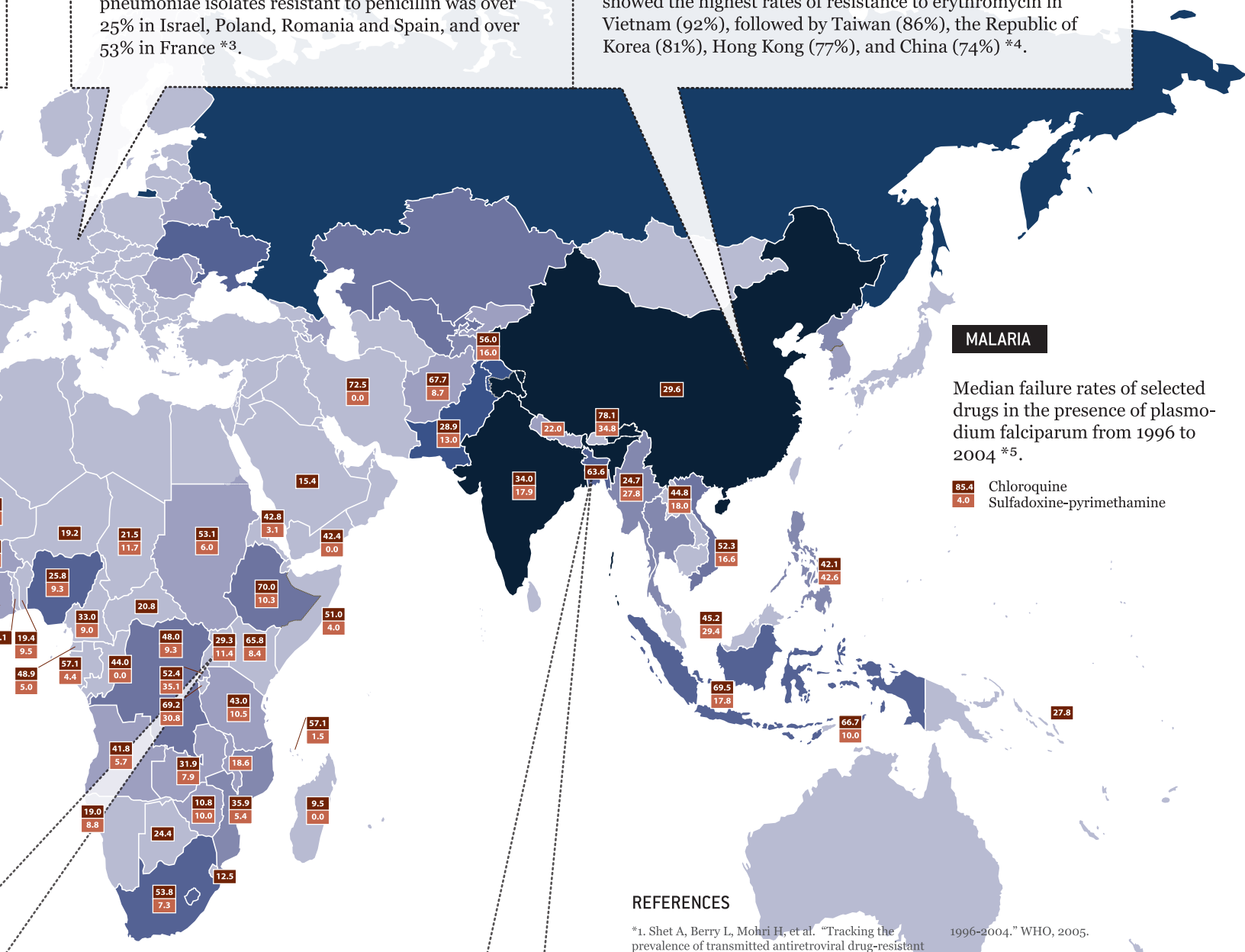
PNEUMONIAE

Europe

In Europe in 2002, the proportion of Streptococcus pneumoniae isolates resistant to penicillin was over 25% in Israel, Poland, Romania and Spain, and over 53% in France *3.

East Asia

Streptococcus pneumoniae isolates from a 2000-2001 study showed the highest rates of resistance to erythromycin in Vietnam (92%), followed by Taiwan (86%), the Republic of Korea (81%), Hong Kong (77%), and China (74%) *4.



MALARIA

Median failure rates of selected drugs in the presence of plasmodium falciparum from 1996 to 2004 *5.

85.4 Chloroquine
4.0 Sulfadoxine-pyrimethamine

Bangladesh

A 1997 study found that 100% of *Shigella dysenteriae* isolates were resistant to ampicillin, tetracycline, and chloramphenicol; while 93% were resistant to ampicillin, tetracycline, chloramphenicol, TMP-SMX, and nalidixic acid *9.

ftriaxone, and azithromycin.

REFERENCES

*1. Shet A, Berry L, Mohri H, et al. "Tracking the prevalence of transmitted antiretroviral drug-resistant HIV-1: a decade of experience." Journal of Acquired Immune Deficiency Syndrome; 41:439-46, 2006.

*2. Hirsch et al. "Antiretoriviral Drug Resistance testing in adult HIV-1 infection: 2008 recommendations of an international AIDS society – USA panel." Clinical Infectious Diseases; 47:266-85, 2008.

*3. Per Nordberg, Dominique L. Monnet, and Otto Cars. "Antibacterial Drug Resistance: Options for concerted action." WHO, Department of Medicines Policy and Standards, February 2005.

*4. Song et al. "High Prevalence of Antimicrobial Resistance among Clinical Streptococcus pneumoniae Isolates in Asia." Antimicrobial Agents and Chemotherapy; 48(6):2101-2107, June 2004.

*5. "Susceptibility of Plasmodium falciparum to antimalarial drugs : report on global monitoring : 1996-2004." WHO, 2005.

*6. "Anti-Tuberculosis Drug Resistance in the World: Report No. 4." The WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance, 2008.

*7. Sivapalasingam et al. "High prevalence of antimicrobial resistance among Shigella isolates in the United States tested by the National Antimicrobial Resistance Monitoring System from 1999 to 2002." Antimicrobial Agents and Chemotherapy; 50: 49–54, 2006.

*8. Legros et al. "Antibiotic Sensitivity of Endemic Shigella in Mbarara, Uganda." East African Medical Journal; 75 (3): 160–1, 1998.

*9. Y Jahan and A Hossain. "Multiple drug resistant Shigella dysenteriae type 1 in Rajbari district, Bangladesh." Journal of Diarrhoeal Diseases Research; 15(1): 17-20, March 1997.

Examples of disappointment in global health are easy to find. The risk of death for children under five years old from acute respiratory infections barely decreased in the 10 years to 2001, despite the increasing use of antibiotics.[7] The proportion of children under 5 with upper respiratory tract infections being treated with antibiotics has risen from 42 percent to 71 percent globally since 1998, but only 35 percent of those children are treated according to clinical guidelines.[8] These connections between inappropriate drug use and poor health outcomes do not provide iron-clad proof of drug resistance as a cause, but it is likely one of the factors.

"A Global-Scale Failure": The Health and Economic Costs of Drug Resistance

The long-term consequences of drug resistance are hard to know, although it has recently been called a "global-scale failure."[9] We do know that the immediate health and economic consequences of resistance are high. The costs of global inaction targeting resistance are borne in the near term by those who are stricken with a resistant disease and lack either access to health services or the financial capacity to obtain the complicated treatment needed. In the longer term, the consequences are borne by all of us—and future generations—who rely on a shrinking collection of effective drugs to cure infectious disease. The emergence of drug resistance puts ever-greater pressure on the successful development of new products, a costly, slow, and uncertain process.

Patients with resistant infections are more likely to experience prolonged illness or to die. They also remain infectious for longer and are therefore more likely to transmit the resistant pathogens they carry. Children suffer the most from drug resistant disease. They are prone to infections and more likely to die or suffer long-term damage if not treated promptly and effectively. The most lethal childhood diseases—malaria, pneumonia and other respiratory infections, and diarrheal diseases—no longer respond to older treatments, and expensive new drugs are often not available in poor countries.

Not only does drug resistant disease have severe health consequences for the patient, but treating these patients further strains weak health systems by imposing additional financial and time demands. Second-line drugs can cost from five times as much (for antiretrovirals) to 175 times as much (for TB drugs) as first-line drugs (see Table 1 in Section 2). These differences already reflect the efforts of health activists and donors to bring down the prices of second-line drugs; in most markets, privately purchased second-line drugs are even more expensive. In addition to the huge price premium for drugs that can at least temporarily overcome resistant disease, the demands on scarce health resources, such as medical personnel, hospital beds, testing kits, and other supplies, all impose very real direct financial and opportunity costs. Finally, donors have been forced to divert funds to pay for more expensive drugs. For AIDS, TB, and malaria, donors are working to make drugs more available and affordable. Between the donor funds allocated through PEPFAR, UNITAID, and the Global Fund to fight AIDS, Tuberculosis and Malaria, over $200 million has already been spent on second-line drugs, and the new Affordable Medicines Facility for malaria (AMFm) anticipates that $1.5 billion will be needed over five years to subsidize artemisinin-based combination therapies (ACTs).

These financial efforts are not reaching even a fraction of the people who contract resistant disease strains, and they are probably unsustainable as the patient burden grows. If one considers that it costs as much to cure one patient of XDR-TB as it does to cure 200 patients of nonresistant TB, society has good economic reason to look for ways to slow, reduce, and contain resistance.

Many Commonalities among Resistance Drivers

There are many drivers of resistance and equally many ways to slow, reduce, or contain it. The prevalence and type of resistance[*] differ from one geographical region to another. The causes of resistance are not uniform across the world or across diseases. Variations in resistance

[*] Meaning which pathogen(s) are resistant to specific drug(s).

development and response derive from different biological modes of action between and among types of bacteria, viruses, and parasites and the various drugs they interact with. Specific disease characteristics also affect the processes through which resistance arises and how much it affects the therapeutic possibilities. Differences in resistance patterns also stem from choices made by governments, health-care providers, and patients. For example, one major factor affecting the prevalence of drug resistance is the sheer availability of drugs. There is a strong link between drug use and the emergence and spread of pathogens resistant to those drugs (both measured at country level).[10] Figure 2 illustrates that close relationship for two antibiotics commonly used in Europe: higher levels of drug use are highly correlated with higher levels of resistance to that class of drug.

But there are also important commonalities in the major drivers of resistance, and in those commonalities lies the greatest opportunity to identify policy solutions. Key drug resistance drivers include inadequate and unavailable drugs and diagnostics; treatment challenges, including adherence; and a lack of health systems infrastructure, including laboratory capacity and public health surveillance systems. These drivers are similar across diseases, yet resistance continues to be addressed vertically disease by disease, through small-scale and uncoordinated efforts.

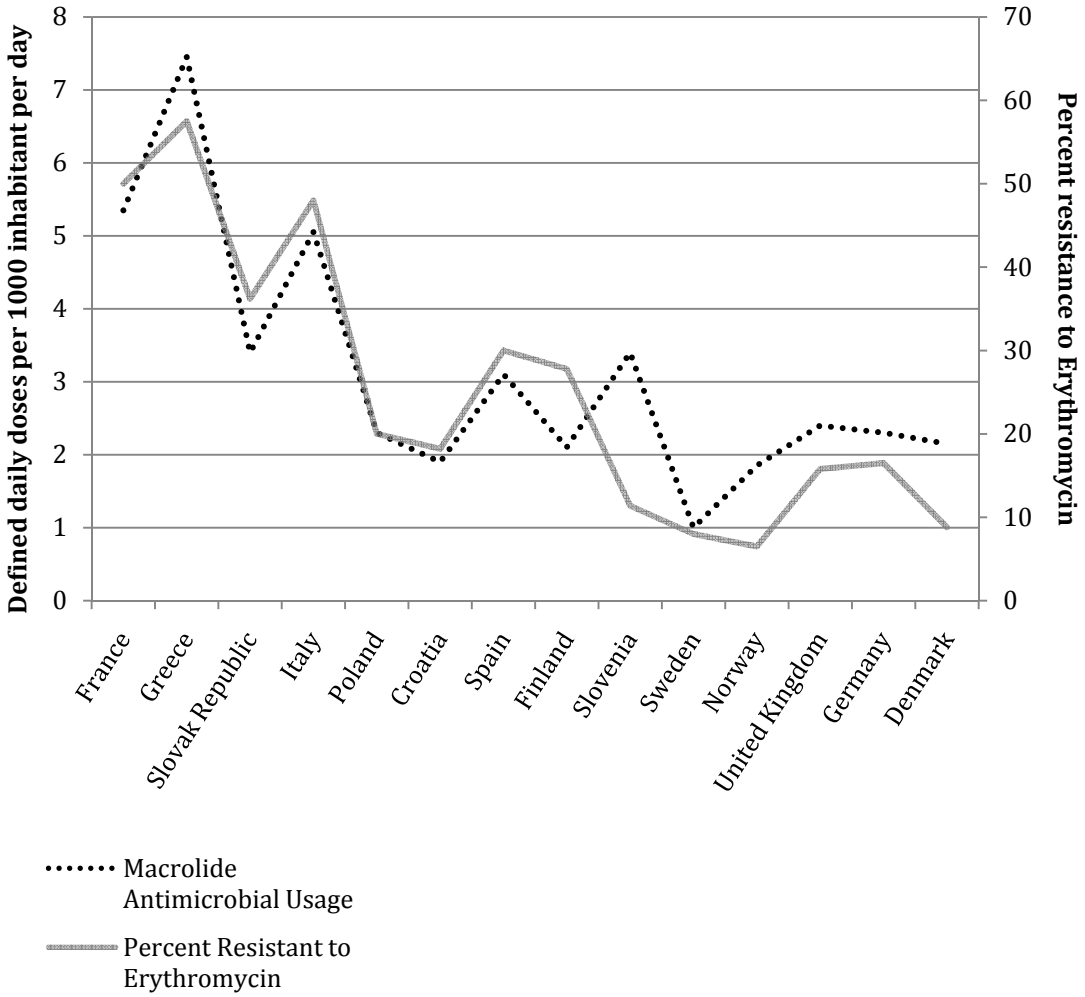
We Can Prevent Drug Resistance

Many of the conditions accelerating drug resistance can be fixed, and the spread of resistance can be prevented or at least greatly slowed. The needed fixes will be more effective if they are applied across diseases. Resistance can be prevented and contained with a combination of the following actions:

- **Know the problem:** a common foundation of better information about resistance, including improved surveillance and laboratory capacity
- **Own the problem: w**idespread incentives to reduce opportunities for resistance

- **Develop new drugs:** strengthened pipelines for new drugs and other technology
- **Use existing products better:** proper use of drugs and diagnostics
- **Lead:** stronger global regulatory and policy leadership

Figure 2. Usage of and Resistance to Selected Antimicrobials in Europe



Box 1 (page 13) describes drug efficacy as a common property resource that is imperceptibly eroded because incentives to protect it are insufficient. This conceptual framing motivates the working group's interlocked set of recommendations to build awareness and incentives for protecting the existing and future curative powers of drug therapy. Slowing drug resistance will require the commitment and action of multiple public and private actors. First among them are

the companies that develop and manufacture drugs and other medical technology—such as diagnostics—that have a responsibility to ensure that their life-saving products are safe and effective and remain so. Governments have a responsibility to provide regulation and oversight of drug licensing, manufacturing, and use. Governments are also the primary providers of laboratory facilities and surveillance systems to detect and monitor when drugs are no longer effective. International technical, financial, and law enforcement agencies have a role to play in providing information and guidance, coordination, financial resources, and assistance in implementing resistance-specific interventions at the country level.

Donors and philanthropic organizations have been active in purchasing and distributing drugs, and they can take a great deal of credit for the surge in drug access and use that has occurred over the past 10 years.[11] These efforts are to be applauded and encouraged, but they need to be accompanied by additional measures to protect and evaluate the effectiveness of drug treatment being offered on behalf of taxpayers and other charitable givers. Drug access is the means to an end—one that should be defined as improved health.

This report offers an integrated set of eight actions to be taken by public and private authorities to deter and defer the global problem of drug resistance. The eight actions are interdependent, starting with the fundamental infrastructure to better understand the problem, moving to changing the behavior of drug users and drug sellers in order to preserve the drugs we already have and to inducements for researchers to come up with new and better drugs. These steps must all begin with stronger global and national leadership to make these actions a priority.

Sections II and III describe resistance to a wide array of drugs used to cure the most serious global diseases, the health and economic burden associated with existing levels of resistance, and the global drivers of resistance. Section IV outlines the piecemeal and insufficient action currently being taken to maintain their usefulness at the global level. Section V proposes the actions needed to better protect current and future populations from resistant forms of disease, and Section VI offers conclusions and areas of future research.

The goal of this report is focus attention on solutions designed to improve incentives to reduce drug resistance, to increase the public goods—such as better information—that are essential to reducing the problem, and to improve the behaviors of people who make countless small decisions to provide and take drugs around the world—decisions that can either assist drug-resistant pathogens to develop or not. For the sake of all people who seek effective health care, now and in the future, and as a core global health priority, drug resistance must be addressed aggressively.

Box 1. A Conceptual Framework for Understanding Drug Efficacy as a Common Property Resource

The curative power of infectious disease drugs (drug efficacy) is not infinite. Natural selective pressure on biological organisms creates new versions of those organisms that can withstand a drug's ability to kill them. Thus, the useful lifetime of a drug is limited by the speed of that evolutionary process, which is determined by many factors. In this regard, drug efficacy exhibits characteristics of a non-renewable resource for which there is an optimal rate of depletion.[12] From society's perspective, this rate is the one at which the value of the resource in use (curing disease now) equals the discount rate (a rate of time preference). In simple terms, do you use the drug now, or save it for later?

Complicating that decision is that inappropriate drug use hastens the evolutionary process described above, thereby creating a negative externality. One person's misuse of a drug has negative consequences for others by helping to create resistant strains and decrease the probability of being cured. Worse yet, a person's misuse of a drug stands a good chance of being useless in treating their own illness. Both these factors illustrate that drug efficacy has social value that must be recognized and protected through government interventions and appropriate institutional arrangements to responsibly manage the scarce resource.

The CGD Working Group's recommendations encourage actions that help balance society's current and future health care needs with the drug and other technologies available, and avoid the unintended negative consequences of individual actions on society. They are based on the premise that actors need information to help them make optimal choices–information about the quantities and types of drugs being distributed and used, where resistance to particular drugs exists, and which choices and behaviors are likely to add to resistance. Providing good information in a timely manner creates the conditions for better informed decisions from drug producers, major drug purchasers, prescribers, sellers, and patients. To move people from informed decision-making to action, the Working Group proposes a set of supportive institutional and programmatic changes that are likely to align individual choices with the dual goals of appropriately valuing existing drugs and creating incentives to develop new drugs.

II. Health and Economic Consequences of the Global Drug Resistance Problem

You have been diagnosed with TB. Treatment is long: you must take a combination of three to four drugs for six months. After struggling through two months of side effects from the medicines, you are finally starting to feel better. Sometimes, you forget to take your drugs at the right time. Then when you go to your local clinic for drug refills, they've run out of what you need. You go to a private seller and buy some drugs that—unbeknownst to you—are of poor quality. The amount of anti-TB drug in your body falls to levels too low to kill all the bacteria . . . and they adapt.

Your persistent cough returns. Individuals in close contact with you are exposed to your now drug-resistant infection. Your niece gets a fever she cannot shake. She loses weight and sweats in her sleep. The local doctor, knowing of your illness, but lacking reliable tests to diagnose TB and identify whether the particular strain is drug-resistant, suspects she also has TB. He prescribes first-*line therapy, since she's never had TB before. What no one realizes is that your niece's TB strain is already resistant to the drugs she will take.*

The drugs required to cure both you and your niece are 100 times more expensive than those you used last time and, since these drugs are not stocked in your village clinic, you must travel regularly to the district capital to collect supplies. That means time off work. Once you get this new second-*line treatment, you'll have to be careful. If the strain you harbor develops resistance to this set of drugs, what options will you have left?*

This situation is all too common in developing countries. The first step to changing it—to effectively fight drug resistance—is to systematically document where drug resistance exists. This section briefly summarizes the most current information available about drug resistance for high-burden diseases in developing countries, how resistance affects treatment of major diseases in the world today and, where possible, its impact on morbidity and mortality. It also describes the economic implications—for patients and for global health donors—of coping with the costs of drug resistance.

What are the Health Consequences of Resistance?

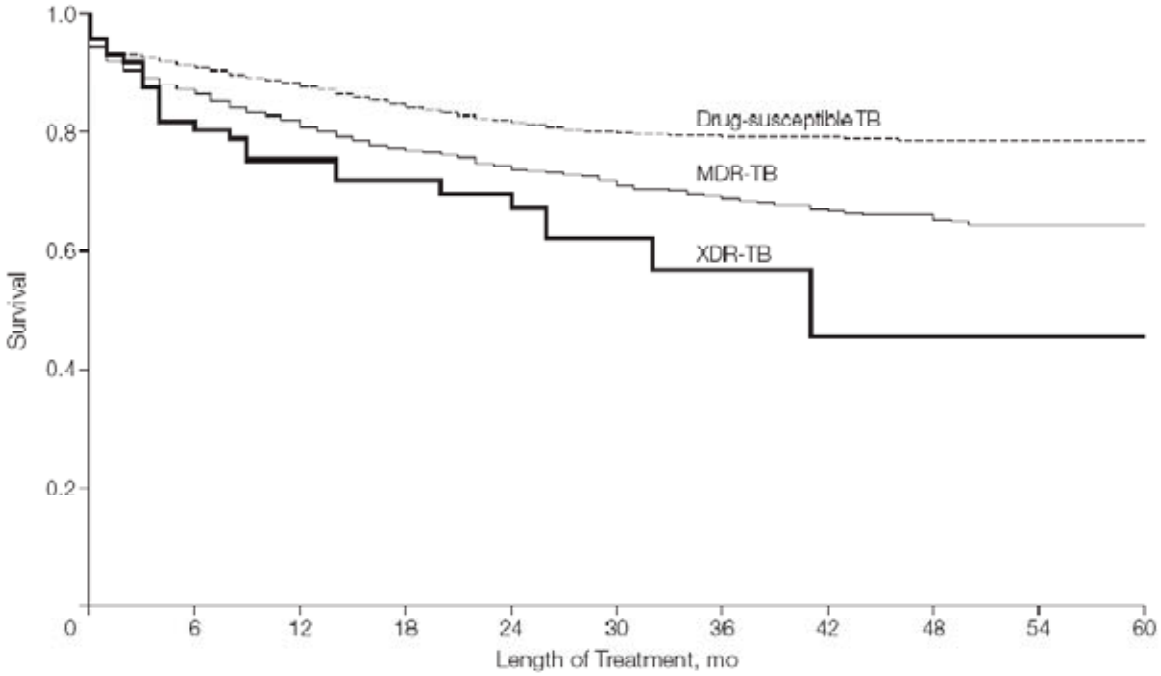
Tuberculosis

TB killed 1.7 million people in 2006. Unlike the short treatment duration for most bacterial pathogens, standard first-line treatment for TB involves four drugs and lasts from six to nine months. This burden, compounded by sometimes harsh side-effects, discourages many patients from completing treatment, which triggers resistance emergence. There are two types of drug resistant TB: multi-drug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB.) [*] As shown in Figure 3's data for the United States, MDR-TB can be treated and about 80 percent of cases can be cured on average, if World Health Organization (WHO) guidelines are followed.[13] For XDR-TB, this number drops to about 60 percent.[14] However, treatment that does not follow the recommended guidelines can lead to higher mortality, increased resistance and further spread of resistant strains.[15]

Drug resistant TB is a global problem. In 2007, there were an estimated 500,000 MDR-TB cases worldwide,[16] of which about 50,000 were XDR-TB cases.[17] Although MDR-TB is concentrated in populous countries such as China, India, and the Russian Federation, which collectively have 57 percent of total cases, the presence of MDR-TB has been detected in almost all countries surveyed.[18] Figure 4 shows the countries with at least one MDR-TB case as of 2007. Areas with fast-rising MDR-TB numbers include the Republic of Korea, Peru, and the Orel and Tomsk Oblasts of the Russian Federation.[19] By September 2009, at least one case of XDR-TB had been recorded in 57 countries,[20] while a July 2009 study found the highest proportions of XDR-TB among MDR-TB cases in Azerbaijan (12.8 percent), Ukraine (15 percent), Estonia (23.7 percent) and Portugal (more than 50 percent).[21]

[*] XDR-TB, a type of MDR-TB which is potentially untreatable with available drugs, is defined as TB caused by *M. tuberculosis* with resistance to any fluoroquinolone and one of the three second-line anti-TB injectables—Amikacin, Kanamycin, or Capreomycin—in addition to isoniazid and rifampicin.

Figure 3: Survival Among XDR-TB, MDR-TB, and Drug-Susceptible TB Cases, United States, 1993-2005



Source: Shah et al., "Extensively Drug-Resistant Tuberculosis in the United States, 1993–2007," *JAMA* 300(18):2153–60.

Given their weakened condition, individuals living with HIV/AIDS are more susceptible than others to developing TB, including drug-resistant TB. Indeed, TB is one of the most common opportunistic infections affecting HIV positive individuals. People infected with HIV are far more likely to die from MDR or XDR-TB than those who are not—some studies show case fatality rates of 90 percent.[22] As many as one-quarter of deaths attributed to TB are in patients co-infected with HIV.[23] Data gaps remain huge, however. For example, Africa has the highest TB incidence of all regions in the world, but only six countries were able to contribute data to the most recent (2008) global report on TB drug resistance. None provided information on TB drug resistance among HIV-positive populations.[24]

HIV/AIDS

Developing country antiretroviral (ART) resistance data are extremely sparse and do not (yet) allow for disaggregation by sub-population or specific risk factors. Studies undertaken by the recently created Global HIV Drug Resistance Surveillance Network* (HIV ResNet) find little evidence of rapid transmission of resistant strains. In studies in Ethiopia, Malawi, South Africa, Swaziland, Tanzania, Thailand, and Uganda, transmitted resistance levels were less than 5 percent in areas where ART has been available the longest.[25] However, increased availability of ARVs is associated with higher rates of acquired resistance and the sheer numbers of individuals who currently receive treatment† and the lack of tools to detect resistance and monitor viral loads suggest that transmitted resistance could become a problem in the future. [26] Additionally, adherence to drug regimens is a particular challenge for life-long ART patients.

Malaria

Malaria kills almost one million children under the age of five annually in sub-Saharan Africa alone.[27] Chloroquine (CQ) was an effective first-line treatment for more than 50 years, but when resistance rates became unacceptably high in the mid-1990s, Sulfadoxine-Pyrimethamine (SP) became the only affordable, effective alternative with few side effects. Parasites resistant to SP emerged almost immediately—indeed resistance to SP was first documented the same year the drug was introduced (1967). Resistance to both CQ and SP, as well as to other drugs such as mefloquine and quinine, now affects most malarial regions of the world. Resistance has also recently been confirmed to some artemisinin-based combination therapies (ACTs), which are the newest and most effective antimalarials, particularly along the Thai-Cambodian border (which is where chloroquine resistance first emerged).[28] If steps are not taken to ensure their correct use, ACTs may suffer the same, short-lived fate of SP. However, there is no treatment to replace ACTs.

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* Which is currently being developed by WHO in collaboration with the International AIDS Society (see http://www.who.int/drugresistance/hivaids/network/en/index.html)

† At the end of 2006, approximately 1.8–2.2 million people living with HIV/AIDS were receiving treatment in low- and middle-income countries

Bacterial pathogens

Current knowledge of resistance to drugs needed to treat common bacterial pathogens is extremely limited outside developed countries. Most comes from small-scale studies by academic and other research or advocacy organizations such as the Alliance for the Prudent Use of Antibiotics (APUA) and the International Network for the Rational Use of Drugs (INRUD), which document local pathogen-specific resistance problems.* However, they all point to a similar conclusion: antibiotics are losing their effectiveness.

Bacterial acute respiratory infections (ARIs) kill more than three million children every year, with *S. pneumoniae* thought to cause up to 70 percent of infections. *S. pneumoniae* strains that can be effectively treated with penicillin have declined to between one-half and two-thirds of the strains circulating in many developed and developing countries, and to less than one-quarter in some. Penicillin-resistant strains have been shown to be more likely to be resistant to other antibiotics as well.[29] Multi-drug resistant *S. pneumoniae* clones that are resistant to penicillin, chloramphenicol, tetracycline, and erythromycin have been isolated. These clones are now thought to be widespread and predominant in parts of Asia (for example in Hong Kong, Japan, and Singapore).[30]

One extremely contagious and often lethal diarrheal pathogen, the *Shigella* bacterium, is estimated to be responsible for approximately 600,000 (mostly child) deaths every year.[31] All four species (*dysenterae*, *flexneri*, *boydii,* and *sonnei*) of *Shigella* have exhibited resistance to antibiotics, and inadequate surveillance to inform appropriate prescribing is rendering treatment ineffective, increasing mortality and morbidity.[32] Drug-resistant *S. dysenterae*, specifically, has been linked to large epidemics and higher death rates in Africa, primarily

* See http://www.tufts.edu/med/apua/ and http://www.inrud.org/; Several notable exceptions have not been sustained. One such example is the Alexander Project, a decade-long international multi-center research program initiated in 1992 which sought to determine how sensitive a variety of common community-acquired lower tract bacterial pathogens, such as *S. pneumoniae*, were to different drugs.

among children.[33] Resistant strains of *S. dysenterae* are also common in Bangladesh, Indonesia, and Thailand.[34]

The Economic Consequences of Resistance

There are important societal consequences of resistance that go beyond health. Resistance has a startling impact on costs. In many countries, expenditures for drugs represent a large proportion of overall health-care costs, constitute the largest out-of-pocket health-related cost for individuals, and they are expected to continue rising with increased demand. In the poorest countries, external funders have spent considerable money and effort to reduce the prices of essential drugs.[*] More than $2 billion is being invested annually in increasing access to key drugs for HIV, TB, and malaria through the Global Fund and PEPFAR alone.[35]

Slowly but surely, the rising need for second- and third-line drugs to treat AIDS, TB, malaria, *S. pneumonia*, shigella, and other prominent diseases afflicting developing countries is undermining recent gains in drug access and price reductions. The following section first describes the price differentials between first-line therapies and second- or third-line therapies for major diseases in the developing world. It then addresses the cost angle from a broader societal perspective, including that of donors.

Resistance increases costs and reduces success of drug treatment

When first-line drugs fail, patients and their health-care providers must turn to costly second- and third-line drugs. With the advent of expanded and innovative donor financing mechanisms to pay for drugs for developing country diseases, prices of many drugs in those countries have fallen dramatically in recent years. But the prices of drugs still on patent—and that means most second- and third-line drugs—are still far higher than for first-line drugs, and are paid either by

[*] See e.g. AMFm announcement from Global Fund, http://www.mmv.org/article.php3?id_article=540

patients directly or by donors and governments on behalf of patients. Where resources are finite or severely inadequate to meet the need, for every person put on second-line treatment, far fewer people can then be given access to life-saving or life-extending care. As a result, donors face greater challenges in meeting treatment targets and excruciating choices about who receives treatment.

Table 1 (next page) shows the multifold difference in price between first-line and second-line drugs for major diseases. It shows that the more advanced drugs needed to treat resistant forms of developing-country diseases cost from 5 to 175 times as much as the first-line drugs. This table oversimplifies the complex international drug markets, where there are vast price differences between branded drugs and generics, for drugs procured through donors for certain countries, under different intellectual property conditions, and other variables. Regardless, whether it is patients footing the bill, or donors, drug resistance vastly increases the bottom line of curing disease.

Drug pricing is a complicated issue, particularly where a market is segmented by multiple buyers and payers. Subsidization lowers the price in the short term, but clearly subsidization cannot continue indefinitely, nor can it reach all patients in developing countries who need these treatments. This section briefly outlines the higher economic costs associated with treating specific major developing country diseases when drug resistance is present.

ARVs

Because of the dominance of donor-funded programs in making ARV treatment available in developing countries, and the influence of advocacy groups in calling for transparency in how treatment is priced, greater information about ARV prices and trends is available than for other drugs. Prices for AIDS antiretrovirals procured by WHO and the Global Fund for poor countries vary widely between generics and branded, and by country.[36] The available price information reveals that there has been a consistent downward trend in ARV prices over the past five years, but a large gap between prices of first-line and second-line ARVs. The WHO published a

Table 1: Cost of Treatment with First-Line and Second-Line Drugs for Major Diseases from Various Sources

Disease	Avg. First-Line Price (USD)	Avg. Second-Line Price (USD)	Ratio of First-line to Second-line Prices
HIV/AIDS[1]	90/patient/year	1,214/patient/year Donor-negotiated: 425/patient/year	Average: ~14x as much Donor-negotiated: ~5x as much
TB[2]	20/course	3,500/course	~175x as much
Malaria[3]	0.25–0.35/adult course (Chloroquine/ SP)	Private: 5-10/adult course (ACT) Donor-funded: 0.20-0.50 in private settings, free or 0.05 in public settings	Private: ~20-40x more Public: rough equivalence

SP = sulfadoxine-pyrimethamine; ACT = artemisinin-based combination therapy

Sources: Waning et al (2009) and AIDS2031 (September 2009), median prices of first- and second-line HAART in low-income countries in 2007. Higher prices prevail in middle-income countries. Lower price shown is available in a limited set of low-income countries through negotiation with the Clinton HIV/AIDS Initiative; Data for 2009 Global Drug Facility supplies from WHO officials at the Stop TB Partnership; Laxminarayan, R. and H. Gellband, 2009, "A Global Subsidy: Key to Affordable Drugs for Malaria?" Health Affairs, July/August 2009.

comparison of first- and second-line ARV treatment costs in 2007 and found that costs of second-line treatment were at least 9 times and up to 17 times more than the costs of first-line treatment on a per-patient annual basis (depending on access to generics).[37] A recent study by AIDS2031 indicates the median price for the commonly used second-line drugs for AIDS patients in 2007 was approximately 14 times the median price of first-line drugs in low-income countries, and more than 36 times the price of first-line drugs in middle-income countries.[38] This situation changed for a select group of countries in 2009. An agreement was negotiated by the William J. Clinton Foundation and Matrix, a Mylan company, to provide a once-daily four-drug combination for second-line treatment of HIV/AIDS available starting at $475 annually in 2009 and at $425 annually in 2010, 28 percent lower than the previous lowest-priced

alternative.[39] These prices are available to a limited number of AIDS patients in the 11 countries working with the Clinton HIV/AIDS Initiative.

There were between 200,000 and 250,000 patients on second-line therapy across the developing world at the end of 2008.[40] These patients account for nearly 20 percent of total ARV expenditures because of the high cost of second-line drugs compared to first-line drugs.[41] These percentages will grow steadily in the coming years as increasing numbers of HIV/AIDS patients experience first-line treatment failure or poor reactions to first-line drugs. One study reported that about 22 percent of AIDS patients switch to second-line therapy after an average of 20 months on first-line therapy,[42] and the number of people on second-line therapy is expected to double by 2011 as patients have longer duration on the drug regimens.

Tuberculosis Drugs

All first-line TB drugs are off-patent and widely variable in price across countries.[43] There are currently only six second-line drugs for TB, and most are too expensive to be in widespread use. Published figures for second-line TB drugs range from 175 to 600 times the cost of first-line drugs for a course of treatment.[44] The Stop TB program at WHO sponsors the Global Drug Facility, which provides second-line TB therapy to patients through public clinics for about $3,500 per course. Country-based anti-TB programs must be approved by the WHO to receive second-line drugs.[*] A large share of the financing comes from UNITAID.

Malaria Drugs

There is wide variation in antimalarial prices across countries, but the most common drugs to which there is widespread resistance in Africa, chloroquine and SP, are priced at $0.20–$0.35 per dose. Currently, subsidized ACTs are being made available through the Clinton Foundation and donors at about twice the price or $0.48 per dose, but unsubsidized ACTs retail for 20 to 40 times as much and their availability across different settings varies significantly.[45] A new global

[*] Through the Green Light Committee.

subsidy for ACTs appears to increase the availability and affordability of antimalarials in target countries.[46]

Antibiotics

There is no simple way to analyze the price differences among first- through fourth-line antibiotics because selection and choice-making criteria are so variable across disease conditions and countries. However, one can relatively easily examine the price differences between new and older antibiotics, recognizing that the few new drugs in existence are often reserved for emergency conditions. As an example, the cost per dose of tetracycline is $0.27 in Uganda, while a newer combination choice of amoxicillin/clavulanic acid costs $8.40 per dose, or 31 times as much.[47]

Donor drug subsidies create access to affordable drugs for many people in developing countries. Efforts combatting the three major diseases—HIV/AIDS, TB, and malaria—each have global donor support for drug purchases. The institutions through which this support is channeled include: UNITAID, the Global Fund for AIDS, TB and Malaria, PEPFAR, and the latest entrant, the Affordable Medicines Facility for malaria (AMFm). The obvious benefits are improved health and reduced mortality of beneficiary populations, as well as reduced transmission of disease, both nonresistant and resistant forms. The additional cost to donors associated with second-line drug purchases prevents millions of additional people from getting immediate access to the drugs they need, and should be part of the tally of the costs of resistance.

Health System Costs of Resistance

Beyond the immediate additional costs of procuring and providing higher-priced drugs, resistance increases the financial burden of delivering health services. A full accounting of the direct economic costs of switching drug protocols should include drug culture and sensitivity testing, procuring and maintaining alternative drug supplies, additional training and demands on health workers, and possible added drug tracking and reporting burdens. For antimalarials

and antibiotics, in particular, the costs of drug resistance are borne directly by the patient, or by developing country governments or national health insurance schemes. Thus the increasing costs of drugs due to evolving patterns of resistance threaten the sustainability of health sector financing across the board. Okeke and Laxminarayan (2005) detail other costs associated with treating resistant diseases.[48]

Smith et al. (2005) argue that drug resistance imposes costs on society beyond the direct health-related aspects, including effects on non–health sector and macroeconomic indicators, such as labor supply and economic growth.[49] These types of macroeconomic costs have not been empirically established due to insufficient record-keeping and lack of trend data. This illustrates one of the complexities of measuring actual economic impacts of resistance as it is difficult to distinguish in a clinical setting the reason for switching a patient's drug protocol, and there can be many constraints on treatment decisions. Outside the clinical setting, additional costs of resistance to the regulatory and policy systems include updates and changes to guidelines and their implementation, regulatory implications, and drug quality inspection and enforcement. These costs have not been tracked.

The only effort to date to estimate broad economic costs of drug resistance was recently published by the European Union.[50] The study included the EU countries, Iceland, and Norway. Costs were divided into in-patient, out-patient, and direct productivity lost from premature mortality. The total annual cost of drug resistance estimated for the region is 1.5 billion euro, or $2.25 billion. This estimate applies only to a selected group of antibacterial agents, and the authors of the study believe it underestimates the full economic costs of antimicrobial resistance.

A narrower U.S. study of the broad economic costs from infections due to drug-resistant *P. aeruginosa* came to $2.7 billion per year.[51] Neither report offers much guidance about the drug-resistance costs to developing countries.

III. Drivers of Drug Resistance

You are feeling better. You've been taking second-line TB drugs for a few weeks now. So has your niece. You have both suffered from some quite strong side-effects of the drugs but the nurses have explained that these are normal and that it is critical that you take the drugs regularly and complete the full course of treatment. If you do so, you'll be in the clear . . . in just a few months.

However, without any signs, the drug-resistant strain of tuberculosis that you and your niece harbored is now lodged inside your cousin, Francis, who just yesterday flew to the United Kingdom. Francis, who was home visiting your extended family during his summer holidays, is now back in London, where he is studying law. When you were sick during his break he helped take care of you whenever he could. He's feeling fine now, excited to begin his second year of studies and see the classmates he missed during the vacation. But he won't feel well for long.

When the coughs start, it takes him a while to connect it to your illness. He puts off going to the doctor. It is the beginning of the year, after all, and there is a lot for him to do. When his night sweats get worse and can no longer be blamed on student housing central heating, Francis finally goes to see a doctor. The doctor examines him and asks about recent contacts and travel. Francis makes the connection. He has the same illness he saw in you when he was home.

The doctor performs a battery of tests. Not only is TB identified, but drug-susceptibility testing accurately determines that the strain Francis harbors is resistant to certain anti-TB drugs, which ensures that the doctor's prescribing decision is appropriately informed and will be effective if he takes the drugs as he is told. If he adheres well to the medicines, Francis, like you and your niece, will be cured of TB in a matter of months.

But how many others has Francis infected with the drug-resistant strain since he left you? Since he became infectious and before he began treatment? And how many of these infected individuals will go undetected for how long? How many other individuals have they, in turn, infected along the way?

A first step to developing a more effective global response to drug resistance is to understand the major drivers. These include a vexing mix of technology gaps, poor information and knowledge, inappropriate behavior, and health system weaknesses. Collectively, these drivers constitute a fertile environment for resistance to take hold and spread. No country or population is spared—one or more of these drivers exist in every part of the world and the global movement of people guarantees that resistant microbes will move with them. All of these drivers must be considered together in developing a comprehensive response to global drug resistance.

A second factor impeding a coherent and systematic response to drug resistance is the specialization of disease communities, particularly at the research and funding end of the spectrum. Well-developed knowledge networks for major infectious diseases exist, and drug resistance is a growing part of the problem definition *within* those networks, but rarely is the topic raised *across* networks of disease specialists in a way that highlights the common drivers and potentially common solutions to drug resistance.[*] The international donor and technical communities as well are siloed by disease and affected population, and few opportunities arise to appreciate the ways in which action across diseases against resistance would improve protection for all drug categories.

While each disease, and even strains of diseases, has specific resistance characteristics, and specific health and economic consequences, the primary drivers of resistance have much in common. The next section expands upon the most significant of these resistance drivers, classifying them into three categories: missing and inadequate technology, harmful drug-selling and drug-using behaviors, and health-system weaknesses.

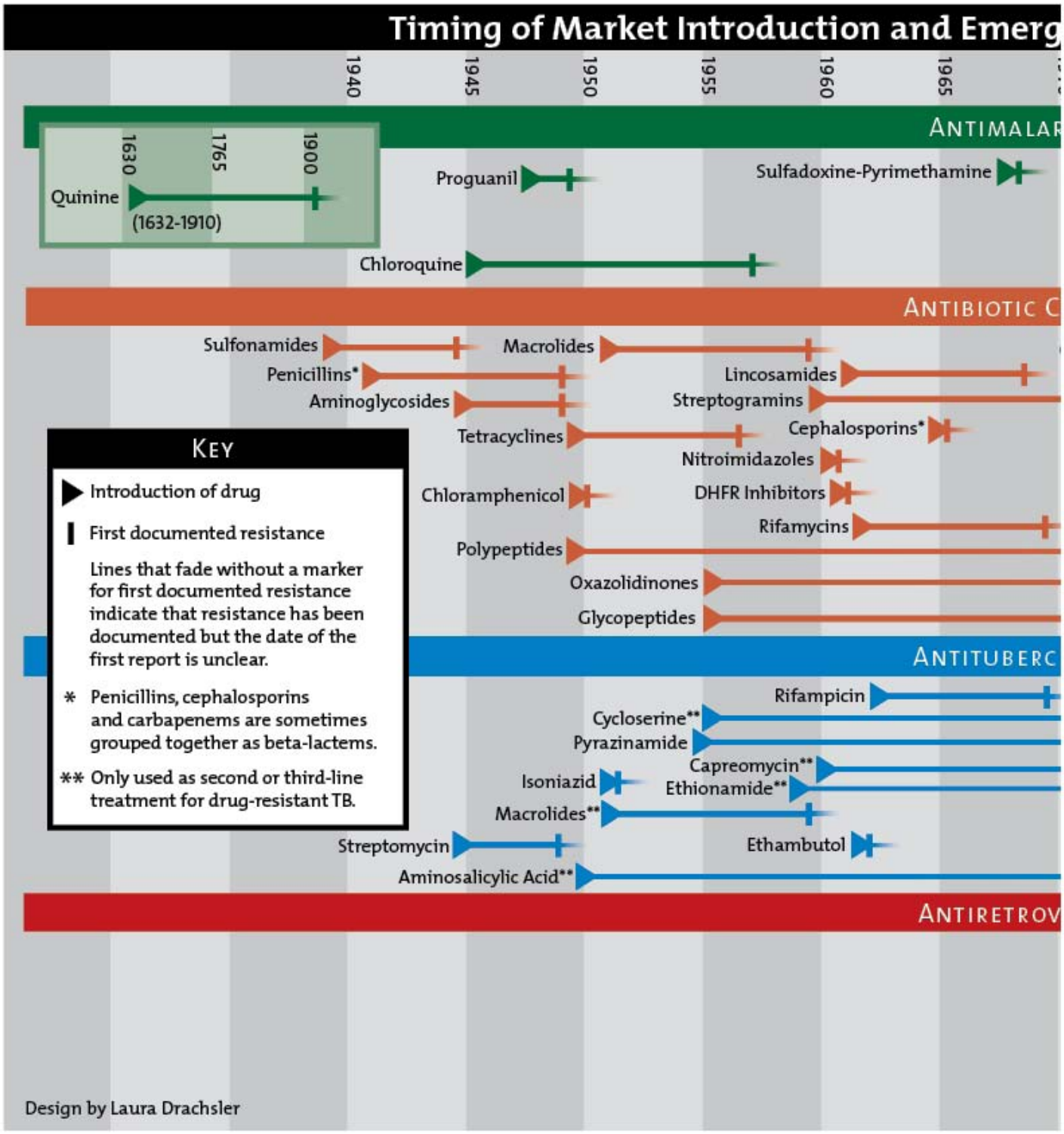
[*] Network analysis article cited in DRWG concept paper

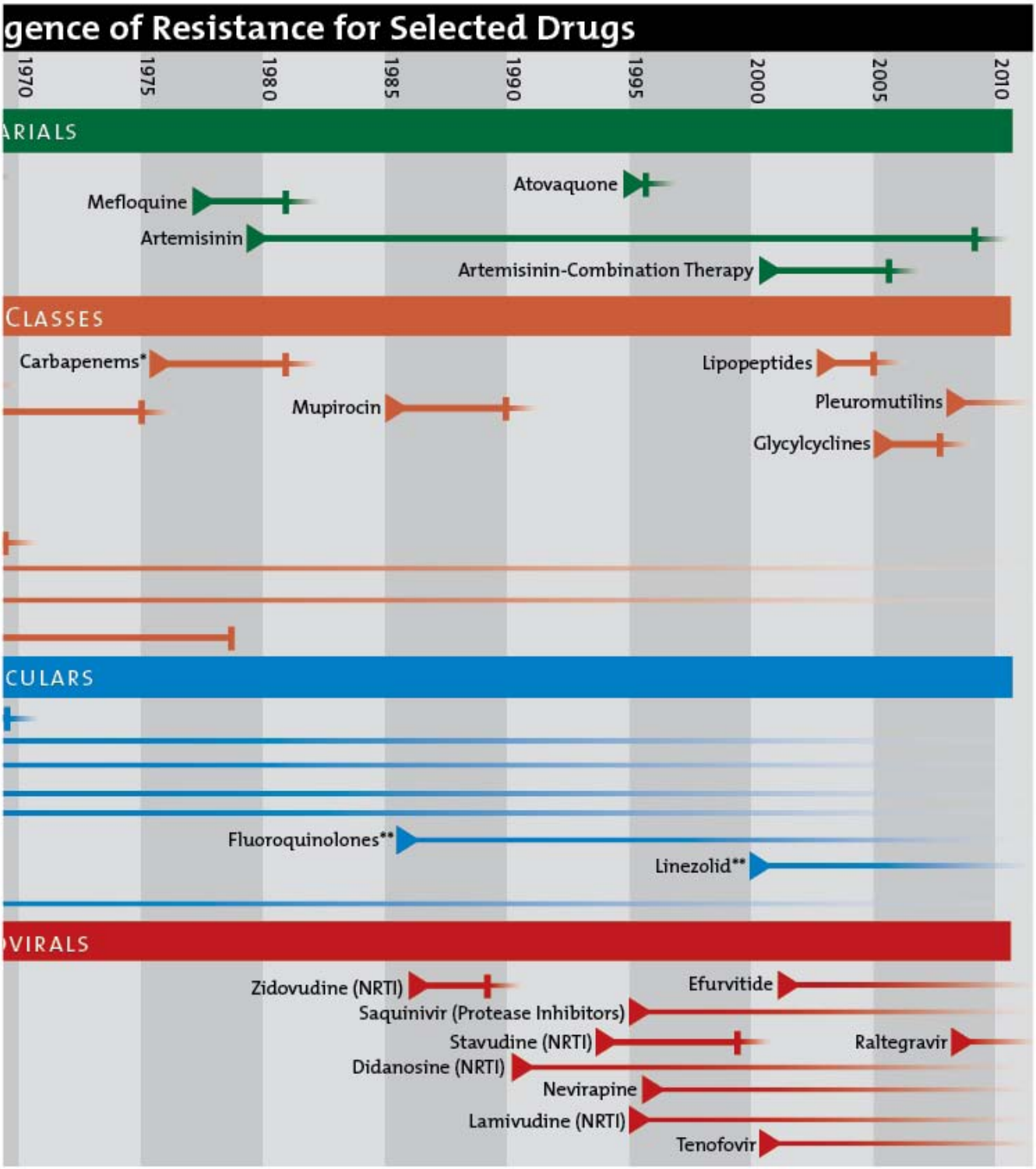
Missing and Inadequate Technology Drives Resistance

New drugs and better diagnostics are a familiar plea in global health. Strenuous advocacy and new funding have advanced research for certain diseases—notably AIDS, TB, and malaria. But expensive new drugs and lab-based diagnostics will not go far enough in countering the effects of resistance. There is still a huge gap between the need and the availability of cheap, rapid, and reliable diagnostics that work at the point of patient contact. Many countries are also awash in poor quality drugs, some of dubious origin, and technologies to quickly and cheaply test them are not being widely used. Perhaps most importantly, new and affordable antibiotics are urgently needed.

History tells us that it is not always easy to generate the technological developments we need to fight drug resistance. In the past decades, many pharmaceutical companies shrunk or sold their infectious disease portfolios as it became clear that stronger profits were to be made in other areas, such as products for chronic noncommunicable diseases like diabetes and Alzheimer's. Figure 4 shows the history of new drug development and subsequent resistance to those drugs in the four major drug/disease categories discussed in this report.

The challenges inherent in treating TB vividly illustrate how drug resistance has eroded the usefulness of current technology. The timeline in Figure 4 shows decades of inaction in R&D for TB. Hence, the microbe has had ample time to evolve resistant strains. Drug-sensitivity testing to determine whether a patient will respond to standard treatment is generally unavailable, and treatment often proceeds on the assumption that the patient does not have a resistant strain.


Timing of Market Introduction and Emerg
1940
1945
1950
1955
1960
1965
ANTIMALAR
1630
1765
1900
Quinine
(1632-1910)
Proguanil
Sulfadoxine-Pyrimethamine
Chloroquine
ANTIBIOTIC C
Sulfonamides
Macrolides
Penicillins*
Lincosamides
Aminoglycosides
Streptogramins
Tetracyclines
Cephalosporins*
Nitroimidazoles
Chloramphenicol
DHFR Inhibitors
Rifamycins
Polypeptides
Oxazolidinones
Glycopeptides
KEY
Introduction of drug
First documented resistance
Lines that fade without a marker for first documented resistance indicate that resistance has been documented but the date of the first report is unclear.
* Penicillins, cephalosporins and carbapenems are sometimes grouped together as beta-lactems.
** Only used as second or third-line treatment for drug-resistant TB.
ANTITUBERC
Rifampicin
Cycloserine**
Pyrazinamide
Capreomycin**
Isoniazid
Ethionamide**
Macrolides**
Streptomycin
Ethambutol
Aminosalicylic Acid**
ANTIRETROV
Design by Laura Drachsler


gence of Resistance for Selected Drugs
1970
1975
1980
1985
1990
1995
2000
2005
2010
ARIALS
Atovaquone
Mefloquine
Artemisinin
Artemisinin-Combination Therapy
CLASSES
Carbapenems*
Lipopeptides
Mupirocin
Pleuromutilins
Glycylcyclines
CULARS
Fluoroquinolones**
Linezolid**
VIRALS
Zidovudine (NRTI)
Efurvitide
Saquinivir (Protease Inhibitors)
Stavudine (NRTI)
Raltegravir
Didanosine (NRTI)
Nevirapine
Lamivudine (NRTI)
Tenofovir

Drug resistance is a naturally occurring, evolutionary phenomenon. The tools we employ to prevent, diagnose, and treat disease must therefore keep evolving too. However, it is not enough to keep pace with changing patterns of resistance—or even to get ahead of the curve. Technological innovations focused on preventing or delaying drug resistance hold promise and should be encouraged. A wide array of possibilities exist for developing new tools, as well as converting existing tools to this purpose in drug and testing procedures, laboratory procedures, and drug-utilization procedures. For instance, resistance can develop when bacterial cells have the ability to destroy a drug or pump it out of their system. Research is underway to develop Efflux Pump Inhibitors (EPIs) that can be combined with an antibiotic to restore its efficacy by stopping bacterial cells from pumping it out. Far greater attention is needed to create incentives for resistant-relevant technology that will increase the longevity of the drug resource.[*] Research and development is the key step in answering those needs, but it must be more intensely focused on impeding the process of resistance development itself.

Beyond the "resistance-reversal" possibilities introduced by new scientific findings, product formulation can be better utilized to deter resistance. Where there is potential for drug resistance to emerge and spread, drugs, diagnostics, and drug-susceptibility tests where appropriate and feasible should be used as an integrated package. However, recently enhanced efforts to develop infectious disease treatments have not been matched by a push for diagnostics or drug-susceptibility tests appropriate to resource-constrained settings.

Diagnostics and drug-susceptibility tests have even smaller profit margins than most drugs. It can be hard, therefore, to motivate pharmaceutical companies to invest in these and other technologies that could help prolong drug efficacy, not least as they may see little commercial rationale for sustaining products beyond their patent term. Public funding and R&D incentives are often required to advance scientific discovery and stimulate private-sector investment.

[*] Further information is at http://www.mpexpharma.com/efflux.html.

TB diagnostics are as important as the drugs themselves. One-third of the world's population is infected with the bacterium that causes TB.[52] Seventy percent of those infected will never get sick, while the remaining 30 percent of infections could become active at some point. Containing the spread of TB requires locating those patients with active TB before they can infect others. Smear microscopy, the detection method most widely used, is no better than a sieve in preventing TB transmission. It must be performed in an equipped laboratory by trained health professionals, and it requires six weeks or more to validate the presence of TB bacilli and repeated interactions between the patient and health system. Finally, the technique has low sensitivity, detecting only about 45 percent of active cases.[53]

The abysmal capacity of TB diagnostic methods to prevent further transmission of the disease and potential spread of resistance is an extreme example, but one with encouraging news. New techniques that can provide faster TB diagnosis are in the pipeline, but they will still require laboratory facilities and expertise in order to be utilized in developing countries.

Behavioral Drivers of Resistance

Many behavioral factors on the patient, provider, and community levels contribute to drug resistance. The incentives driving patients, providers, and communities often do not lead to socially optimal behavior (in this case rational drug prescribing, dispensing, and use).

Patient drug choices are affected by the costs of accessing health care, including drugs. Where services are costly or too far away, patients often have the incentive to select the drugs themselves. Self-medication may lead to use of the wrong drug or less than the required full course of a correct drug. Informal dispensers of drug medicines are estimated to be the most common source of drug access for a large percentage of the world's population. A recent review addressing malaria treatment in sub-Saharan Africa found, for example, that 15–83 percent of caregivers sought treatment and advice for childhood illness in shops, rather than from a health facility.[54] In those outlets, medicine is often sold in small units so that it is more affordable than purchasing a complete regimen.[55]

In addition to costs, many other factors contribute to poor treatment adherence among patients. They include strong side-effects of the drugs, complex treatment protocols, or simply feeling better after taking a partial treatment. All contribute to behaviors that favor resistance development.

Stigma as well influences patient behavior in ways that lead to irrational drug use. For example, individuals may choose to go to informal, untrained and unregulated providers or not seek any health services at all if they suspect they have a sex- or poverty-linked disease such as HIV or TB.[56] If a patient does seek health care, they may experience discrimination in the form of poor referral practices; for example, HIV positive patients (in particular homosexual men or intravenous drug users) may be viewed as "to blame" for their condition and not be promptly referred by health providers (for TB diagnosis and treatment for example). Stigma can also be a direct barrier to drug adherence.[57] For example, when stigma prevents patients from disclosing their HIV status, it becomes difficult for these patients to take pills in public.[58] In such situation patients also lack adherence support from close family or friends.[59]

In many parts of the world, cultural preferences and beliefs (such as higher effectiveness of multi-colored capsules over plain ones or injectables over pills) affect individual drug-taking behavior.[60] Local leaders and their role in defining culture and habits can play a determining role in patient adherence; for example, in one study from India, 50 percent of HIV-positive patients who were referred to specialist centers for not responding to treatment had stopped taking ART on the recommendation of a traditional healer.[61] Gender-related issues may also play a role in behavior. For example, in some societies it is inappropriate for a woman to travel unaccompanied by a male; frequent trips to a health clinic might therefore prove problematic. In many countries where women's health needs are given lower priority than those of others in the family, female patients may share their prescriptions with their husbands and children.[62]

Poor incentives and training among health-care professionals can inadvertently and sometimes subtly allow resistance to thrive. Many of these factors are a normal part of health-care practice in both rich and poor countries and are not commonly recognized as contributing to drug resistance. Because the incentives influencing provider behavior can be very complex, it is crucial that interventions are designed with an understanding of the factors motivating current prescribing and dispensing behavior.

For example, difficulty in diagnosis and a lack of information to support drug selection lead doctors and other prescribers to choose the wrong drug or the wrong amount of a drug, both of which drive resistance. Clinicians sometimes do not follow the results indicated by a diagnostic test, because of real or perceived inadequacies of the technology.[63] It is not uncommon for a provider to feel (real or perceived) pressure from the patient to treat. Under such circumstances, the provider's incentive is to satisfy the customer and simply prescribe a drug and "close the transaction," on the principle that this leads to a better relationship and a better chance that the patient will return when a new illness or episode occurs. Other factors that drive behavior during the patient/provider interaction include a patient's expressed desire for a given drug (often as a result of industry advertising) and whether or not the provider councils the patient about appropriate drug use (hence possibly detecting and discussing a potential adherence problem).

Receiving payments for dispensing a given drug can also exert a strong influence on provider behavior, especially where prescribers are also drug dispensers. Providers who make a profit from drug sales (or just from the consultation that accompanies a drug hand-out) have the incentive to make a "transaction." Providers in many Asian countries, for example, often receive a good part of their income from drug sales, in particular broad-spectrum antimicrobials, rather than from services charges.[64] The incentive to overprescribe is obvious. In China, for example, recent health-sector reforms have resulted in 100,000 public hospitals being allowed to generate revenue from drugs sold. Attention to the effect of this change on drug resistance is essential.

Industry pressure to prescribe and dispense certain drugs can additionally influence provider behavior. For example, one pharmaceutical company in India distributed leaflets recommending the use of rifabutin for MDR-TB, which is neither in line with the recommendations of the Indian public TB authorities nor with international guidelines.[65] Similarly, a drug company in India placed misleading pictures on the outside of the drug box about what its drug could be used for.[66]

Health Systems Drivers of Resistance

Drugs move through complex supply chains from manufacturer to dispenser to reach patients. Along the way, there are numerous opportunities for drug resistance to flourish, and patients often pay the price, receiving an inaccurate diagnosis or ineffective medicines. The main points of entry for resistance derive from insufficient or ill-trained health professionals, weak or non-existent infrastructure, and lack of regulation or enforcement. Each has a distinct role in preventing and detecting drug resistance, but none can do so in isolation.

Where trained health workers are in short supply, it is far harder to ensure that drugs are prescribed, dispensed, and used appropriately. The critical shortage of health workers—particularly across Africa—is now widely acknowledged and receiving attention. Relevant global partnerships and other donor-financed initiatives have tended to focus most heavily on increasing developing countries' ability to train and retain doctors, nurses, and midwives.[*] This should have a significant impact in improving quality of care and patient outcomes. However, somewhat less attention has been given to the two other professional groups vital to protecting drug efficacy: laboratory health workers and pharmacists.[†]

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[*] The most relevant partnership example is the Global Health Workforce Alliance (GHWA) http://www.ghwa.org/; WHO, "New global alliance seeks to address worldwide shortage of doctors, nurses and other health workers," press release, Geneva, 25th May 2006 http://www.who.int/mediacentre/news/releases/2006/pr26/en/index.html. The creation of the GHWA followed the release of the 2006 World Health Report Working Together for Health: http://www.who.int/whr/2006/en/index.html. For a donor-fianced initiative, see for example International Health Partnership and other initiatives (IHP+) http://www.internationalhealthpartnership.net/.

[†] Defined by WHO for the Global Atlas of the Health Workforce as including 'laboratory scientists, laboratory assistants, laboratory technicians, radiographers and related occupations.' Some interesting exceptions to this rule

Laboratories are perhaps the most neglected of all health system components in developing countries, and have been termed the "Achilles Heel" of global efforts to combat infectious diseases.[67] Without a competent and interlinked laboratory network for countries to turn to, public health surveillance and control are operating blindly. Human resource constraints are a particular issue, but other capacity and organizational issues prevent effective lab support to track and fight resistance.

The shortage of lab workers is most acute in Africa. In 2008, Sierra Leone had just 43 laboratory technicians and assistants in the entire country; Senegal had 90, and Ghana 213.[*] Laboratory workers often lack necessary training and equipment, and since their capacity for testing and analysis is so weak, clinicians can be reluctant to use laboratory diagnoses.[68] This is one reason clinicians rely on symptomatic diagnosis to prescribe drugs. The same poor or non-existent lab capacity discourages clinicians from requesting drug-susceptibility tests (DST) and, when they do, results are seldom timely. Now, even though simple microbiological techniques can be used to determine drug susceptibility for most bacteria, many countries have—at best—one or two laboratories with such capacity. Once a sample is sent away, it can take several months for a result to come back. Indeed, one study on MDR-TB in Peru found that it took on average nearly five months for a patient to be put on appropriate treatment when DST was undertaken by a central laboratory.[69] If a patient remains on ineffective therapy during such an extended period, it prolongs their suffering (leading to death in some cases) and increases the risk they will infect others.

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include the donor-supported six-year Emergency Human Resources Programme in Malawi, which included targets for recruiting both pharmacy and laboratory technicians, and 11,000 'health surveillance assistants' (Source: McCoy, D, McPake B and Mwapasa, V 'The double burden of human resource and HIV crises: a case study of Malawi' Human Resources for Health 2008, 6:16); and the recently launched high-level Taskforce to identify and promote innovative financing mechanisms for health results in poor countries, with strong emphasis on human resources for health, which has not specified any focal professional cadres as yet. (See DFID press release at http://www.dfid.gov.uk/news/files/pressreleases/investment-global-health.asp)

[*] Source: Global Atlas of the Health Workforce (http://www.who.int/globalatlas); accessed 17th September 2009.

Another consequence of weak laboratory capacity is a lack of public health surveillance. Trends in drug use or drug resistance are not routinely monitored in most developing-country settings and record-keeping in public health laboratories is often limited. As a result, current drug resistance data are extremely patchy. Trends can be inferred only with caution from the discrete research projects and testing of limited samples by disease-specific reference laboratories far from the point of care. It is very difficult, therefore, for health workers or policymakers to respond appropriately to the challenge of drug resistance beyond encouraging rational drug use.

Drug dispensing is a multifaceted business in most developing countries, with drugs dispensed by hospitals and clinics, private doctors, community pharmacies, and by informal-sector drug sellers. As described in the preceding section on behavioral resistance drivers, the quality of dispensing practice varies widely but is generally low in many settings.[70] Many informal-sector providers are unregulated, though in some countries efforts have been made to license them and to introduce quality control measures. Running out of stock of drugs and other supplies is a problem, particularly in the public sector.

Meanwhile, many qualified and registered pharmacists perform limited roles in practice and are frequently constrained to basic dispensing functions. In a busy pharmacy, with no or few support staff, pharmacists lack time to educate or counsel patients on issues such as adherence. They also lack up-to-date training in appropriate drug use and drug resistance. Finally, incentive structures within pharmacy practice and the broader health system frequently encourage rapid dispensing of large quantities of medicines, rather than providing high-quality patient care. All of these factors contribute to an environment in which drug use is suboptimal and may fuel the emergence and spread of drug resistance.

Accurate pharmacy workforce assessments are difficult to obtain, but the International Pharmaceutical Federation (FIP) periodic surveys suggest pharmacy services in the world's poorest countries are acutely stretched. In many countries, the number of pharmacists

graduating each year is too low to significantly expand the cadre, particularly as many emigrate. For example, in Ghana, almost two-thirds of the 140 pharmacists graduating in 2003 left the country.[71] Chad, with a population of over 10 million, had just 44 pharmacists practicing nationwide in 2009 and no new graduates at all.[72] With so few qualified pharmacists available, many patients obtain their drugs from dispensing outlets staffed by other health professionals (such as nurses) or by untrained "chemical sellers."

Regulatory oversight is a third critical component of a health system's capacity to protect drug efficacy. Regulation of the pharmaceutical supply chain—from the point of drug development and manufacture right through to when the drug is dispensed to the patient—is fundamental to improving access to medicines in developing countries and to ensuring that drugs are prescribed and used appropriately.

Drug quality is a critical concern and a responsibility of both drug regulators and manufacturers. To be effective and prevent resistance, drugs must contain the appropriate amount of active ingredients. Substandard drugs contain a sub-therapeutic amount of required active ingredient because of poor-quality manufacturing, packaging, transportation, or storage conditions, or as the result of outright counterfeiting.* It is sometimes hard to distinguish substandard drugs from counterfeits, but the WHO estimates 30 percent of drugs sold in Africa are counterfeits, and a recent study in five African countries and India found that 41–47 percent of drugs sampled did not meet all quality standards.[73] The UN Office on Drugs and Crime also recently

* Where "substandard" is defined as products that do not meet internationally accepted standards of identity, strength, purity, and quality. Substandard drugs may or may not be counterfeits (an example of noncounterfeit drugs are those that were properly manufactured, but have deteriorated due to poor packaging, transportation, or storage). "Counterfeit" means a drug that has been deliberately manipulated or made to resemble a specific (normally branded) product on the market. The drug that has been manipulated may contain a sub-therapeutic amount of active pharmaceutical ingredient (and thus also be substandard, possibly contributing to resistance emergence), no active ingredient (which clearly is not beneficial to the patient, but does not drive resistance) or an inappropriate active ingredient (which is also clearly not beneficial to the patient and may or may not drive resistance).

reported that 50 to 60 percent of anti-infectives tested in Africa and Asia had insufficient quantities of active ingredient.[74]

Protecting drug quality and efficacy is costly and technically demanding, especially to developing-country governments struggling to improve the health of their populations with inadequate resources. It is a complex task that requires a combination of scientific, legal, industrial, and law enforcement expertise, many of which are in rare supply in developing countries. In some countries the expertise is distributed across multiple agencies, further complicating the task. Thus, for many reasons—institutional, political, and resource constraints—there is variability in the capacity of national regulators to accomplish their duties and a pressing need to accomplish more with limited resources.

National drug regulatory agencies (NDRAs) have multiple opportunities to protect the supply chain from drug resistance, such as through clinical trial regulation; market authorization; quality assurance at the importation/wholesale level; quality control at dispensing facility level; pharmacovigilance efforts;* regulation of drug promotion; and inspection of pharmaceutical manufacturers, healthcare providers, and dispensing outlets. NDRAs in many countries are critically underresourced and do not fulfill many of these functions. For example, pharmacovigilance is absent from most developing countries: only 27 percent of low- and middle-income countries undertake any formal pharmacovigilance, while 96 percent of high-income countries carry out this work. Often, revenue-generating activities such as drug registration are prioritized at the expense of regulatory enforcement across the local pharmaceutical market. Several small countries have no national agency at all and rely instead on upstream decisions (e.g. market authorization or its withdrawal) by agencies in neighboring countries.

* Pharmacovigilance (PV) is defined by WHO as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems." Such problems might include drug interactions (including between allopathic and herbal or traditional medicines), off-label uses, and the presence of substandard or counterfeit products on the market, as well as reported lack of efficacy.

The result in many resource-limited settings is a largely unregulated pharmaceutical market—a drug bazaar actually—where substandard and counterfeit products circulate freely, and where adverse patient reactions to drugs are rarely documented. There are serious gaps in the available information about what drugs are circulating in countries and who is making them. For instance, there is often only scattered knowledge of where second-line drugs are circulating.

This minimally regulated environment drives the emergence and spread of drug resistance in many regions of the world. A country's policies and actions (or inactions) to regulate its drug supply also affect other countries, even well beyond its immediate borders. Problems arise when countries take different approaches to regulatory enforcement. Countries may be tempted to neglect some of the steps needed to protect and ensure proper use of their drug supplies, in effect hoping to free ride on the efforts of other countries. Unfortunately, this behavior easily becomes a vicious cycle of inaction and finger-pointing that prevents cooperation among countries and may encourage a "rush to the bottom."

Resistance arising from non-human drug use

A final, yet very important, driver of drug resistance in humans is our collective approach and continued behavior towards animal health. Veterinary drug use is relevant here, but of greatest concern is the use of therapeutic and sub-therapeutic levels of antibiotics in agriculture. Sub-therapeutic use in food animals (i.e. deriving from the financial incentives of being able to promote rapid growth and earlier marketing, and to reduce the incidence of disease and thereby cut costs) is particularly controversial. This practice has been widely prevalent in industrialized countries, although there have been attempts to address it for nearly 40 years.[*]

[*] Studies on the use of antibiotics in food animals have been undertaken by bodies such as the Food and Nutrition Board and the National Academies since the early 1970s.

Recent evidence from Canada, the United States, and Europe suggests the problem of antibiotic overuse and emergence of antibiotic resistance in animals is even more severe than previously acknowledged. For example, the Union of Concerned Scientists estimates that at least 70 percent of all antibiotics consumed in the United States are fed to animals on factory farms, while a recent study from the U.S. Centers for Disease Control and Prevention (CDC) suggested that more than 20 percent of human MRSA infections in the Netherlands derive from an animal strain.[75]

Less is known about the extent of antibiotic use in livestock across Africa, Asia, and Latin America. However, as agricultural production becomes increasingly industrialized it is likely that usage will increase. Indeed, Nigerian research indicates high rates of antibiotic use in poultry and livestock and significant prevalence of resistant strains of bacteria in both animals and their feed. Several examples of recent findings follow:

- *E. coli* isolates from chicken in South West Nigeria demonstrating 19 different resistance patterns to 12 different antimicrobial agents[76]
- *Salmonella* isolates from poultry feed in Imo State, Nigeria, demonstrating high resistance (51–100%) to nitrofurantoin, ampicillin, tetracycline, and ceftriazole, and moderate resistance (31–50%) to chloramphenicol, ofloxacin and cotrimoxazole. Low rates of resistance were also found to several other antibiotics[77]
- Streptomycin residue found in goat, pig, and cattle meat sold for human consumption in South West Nigeria, sometimes at potentially toxic concentrations[78]

In the area of animal health, there have been some limited gains in recent years. Antibiotics in animal feed have now been banned in Europe.[79] In the United States, when the use of fluoroquinolones in poultry was found to have contributed to the significant growth in fluoroquinolone-resistant strains of *Campylobacter* in humans, efforts were made to ban this practice. The ensuing legal process lasted five years, culminating in a ban effective from September 2005.[80] However, public health success stories of this type are rare. In addition,

collaboration between experts in animal and human health is limited—a recent and notable exception being the case of avian influenza.[*] The ongoing swine flu pandemic (2009 H1N1) may have added further impetus to collaborative endeavors across the two professions.

This issue is discussed further in Section VI on needed research.

[*] Another example is the "One World, One Health" initiative, led by the World Conservation Society, which brings human and animal health experts together through regular symposia and other means, to discuss shared agendas. http://www.oneworldonehealth.org/

IV. The Current Response

Technical experts in the global health community have previously identified and advocated for a wide range of actions to slow the emergence and spread of drug resistance. [*] However, previous recommendations have been unsystematically and inconsistently pursued. Actions are primarily disease-specific and rarely taken to scale. A safe and efficacious drug supply turns out to be one more casualty of silos in health care—particularly where donors are involved—that lead to partial and inadequately financed solutions, often with treatment of only a single disease in mind. The presence of drug resistance sufficient to limit the ability to treat one disease is a warning that drug resistance to other diseases either is already present or could emerge, since effective treatment delivery relies on common foundations.

There is an exception that demonstrates what is possible in protecting the efficacy of drug supplies. Impressive attention and funding for HIV/AIDS has provided many resources that are unavailable to other diseases and conditions—including dedicated laboratories and trained health workers, failsafe supply chains, health information systems, and patient counseling and adherence support. Partly as a result of so much attention to the three drivers described above—adequate technology, behavioral needs, and health-systems support—the amount of resistance to AIDS drugs is relatively low so far. It should be feasible to build upon that success by extending to other diseases some of the valuable procedures and systems in place to treat AIDS.

Leadership is missing

Drug resistance presents a significant and growing challenge. Strong leadership is needed to address it, both within countries and among global technical and funding organizations, as well as from the private sector. Because the success of all infectious disease treatment efforts

[*] A compendium of prior recommendations from major studies and organizations was prepared as background to this report and is available at http://www.slideshare.net/cgdev/j-pickett-recommendations-3-7-presentation/

depends on maintaining the efficacy of existing drugs, efforts to recognize and prevent drug resistance will be most effective if they are integrated into all treatment programs.

At the global level, the WHO has a critical and unique role to play. It has consistently tried to bring greater attention and funding to the prevention of antimicrobial drug resistance through education and promotion of good practices—with little success. In 2001, the WHO launched a global strategy on antimicrobial resistance (AMR). Its goals were reinforced by two World Health Assembly resolutions: one in 2005 on AMR and another in 2007 on rational drug use. Implementation of the strategy by member states has been patchy, and direct support by donors is extremely limited. AMR has also been selected as the Third Global Patient Safety Challenge, which is due to launch in 2010.[81] As yet, however, there is no evidence that resources will flow to this or other areas of WHO's work on drug resistance and rational drug use across diseases. On the contrary, in recent years the WHO has emphasized technical work on drug resistance only on a disease-specific basis, with an increased emphasis on drug-resistant TB.[82]

The WHO has played a more central role in drug quality and safety, as well as disease surveillance—all areas relevant to tackling drug resistance. It hosts the International Medical Products Anti-Counterfeiting Taskforce (IMPACT). It also manages the UN pre-qualification program, which evaluates the quality, safety, and efficacy of medicines for HIV, TB, malaria, and reproductive health, principally to facilitate bulk procurement by UN and other agencies.[*] Both responsibilities put the WHO in a strong position to monitor and disseminate information about drug efficacy globally—which is an essential contribution to the global public good.

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[*] Recently, NDRAs in resource-constrained settings have been urged to rely on WHO pre-qualification and the decisions of stringent NDRAs—i.e. those that are members of the International Conference on Harmonization (ICH) or PICs—rather than undertake their own inspections and studies to inform market authorization. Many NDRAs are reluctant to do this, partly because of concerns about a loss of market control and a perceived loss of sovereignty. There are resource implications as well, as many NDRAs derive a significant proportion of their financing from fees levied during the drug registration process.

The WHO has an additional role in responding to and conveying information as the sponsor of the International Health Regulations (IHRs), an enforceable system for notifying public health officials about disease threats of potential international concern. In the most recent version (IHR 2005), clear provision is made for reporting the emergence or spread of drug resistant pathogens, particularly where the disease in question is already prevalent across the sub-region. However, there is no evidence that the IHRs have been used to notify countries of drug resistance to global diseases—not least because much of the discussion between WHO and Member States under the auspices of the IHRs is confidential. Two examples of current resistance-related global health threats—XDR-TB and Tamiflu-resistant influenza—are deserving of notification and monitoring under the IHRs. The lack of capacity in many countries to detect cases of drug-resistant disease seriously undermines the usefulness of the IHRs, and the WHO's important role as an information-gathering body for global health.

Alongside the WHO, a handful of other public and nonprofit organizations attempt to raise awareness about and respond to drug resistance—primarily trying to provide information and education. Despite laudable persistence and commitment, they are not able to fill the leadership void, nor gather sufficient information to generate the needed attention to the problem. They are all either small organizations with small budgets, or small offices within large organizations with little leverage to bring the issue to higher-level authorities. The most active among these are ReAct, the Alliance for the Prudent Use of Antibiotics (APUA), the U.S. Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC).[*] A number of disease-specific global networks focused on drug resistance have also been formed. Examples include the International Collaboration on Gonococci (ICG), the HIV ResNet, and the new WorldWide Antimalarial Resistance Network (WWARN). These networks have played an important role, for example in developing guidance on drug resistance surveillance and gathering available data. However, they are severely underresourced relative

[*] The ECDC is significantly enhancing its drug resistance prevention. One program tracks rates of antibiotic usage in Europe (http://app.esac.ua.ac.be/public/) and another works on harmonizing drug-susceptibility testing across Europe (http://www.eucast.org/).

to the scale of the problem. Their vital efforts are maintained by a handful of dedicated individuals (who spend much of their time securing financing to support the next phase of their work). This is clearly unsustainable.

Only a few donors have demonstrated awareness of drug resistance as a global problem with the potential to undermine their global health programming. The U.S. Agency for International Development (USAID) and the Swedish International Development Agency (SIDA) are among the very few bilateral donors that have provided limited resources to improve the use of antibiotics in developing countries. The box below sets out some other examples of donor programming on drug resistance.

Box 2. Examples of donor-supported efforts to address drug resistance

The case for donor action to tackle drug resistance is compelling. Drug resistance is already undermining donor investments in improving public health and access to medicines in developing countries. It is also clear that concerted, collective action is needed to address this increasingly globalized problem, and developing countries will need financial and technical assistance to play their part.

Until now, donors have worked on drug resistance issues in a piecemeal fashion, or have supported medicines initiatives in related areas but with little or no specific attention to the challenges of drug resistance

- Bilateral Donors
    - The UK's Department for International Development (DFID) supports many medicines initiatives not specific to drug resistance, e.g. the Medicines Transparency Alliance (MeTA), and the new Southern Africa Programme on Access to Medicines and Diagnostics (SARPAM). In the past, it supported short-term antimalarial resistance surveillance through the East African Network for Monitoring Antimalarial Treatment (EANMAT). DFID also makes significant investments in health technology R&D and has funded resistance-related research through e.g. LSHTM for MDR-TB rapid diagnostics;
    - The Netherlands is another important funder of pharmaceutical policy and supply chain management efforts, and has supported HIV/AIDS resistance monitoring through LAASER; while Sweden has demonstrated significant leadership domestically in tackling drug resistance, for example through the Swedish Strategic Programme Against Antibiotic Resistance (Strama). Most recently, Sweden instigated efforts to form a transatlantic task force on antimicrobial resistance, which was announced in November 2009. Details on

the task force's scope, duration and composition are yet to emerge, but it is hoped that it will address drug resistance from a global health perspective.
    - USAID's work on medicines focuses on the management of pharmaceutical supply systems. This includes support to antimicrobial resistance (AMR) tracking and rational medicines use. USAID also funded MSH to develop a new AMR program implementation manual based on the 2001 WHO strategy. Other activities are determined by country missions drawing on the strategic framework from the US Government's Strengthening Pharmaceutical Systems program;
- Private philanthropic foundations
    - The Bill and Melinda Gates Foundation has been the most active on drug resistance issues, supporting the Grand Challenges Explorations on basic scientific research, as well as drug resistance surveillance (the WorldWide Antimalarial Resistance Network) and new drug development through Product Development – Public Private Partnerships (e.g. for TB and malaria).
- Multilateral donors
    - The World Bank is increasing its investments in health infrastructure vital to tackling drug resistance, such as laboratory capacity;
    - WHO provides a small but steady flow of resources to maintain an office on antimicrobial resistance, but has made drug resistance a central focus of its TB work program and has strong technical expertise in several other disease areas with a focus on resistance. Antimicrobial resistance is also the theme of the current Patient Safety Challenge at the WHO.

In addition to the programs highlighted above that specifically relate to drug resistance, global health agencies and funders (and many others not listed here) influence drug efficacy in numerous potentially beneficial—but also potentially harmful—ways. For example, beneficial effects derive from efforts to ensure drug safety and quality (e.g., the USAID-supported USP Drug Quality Information program) and to build laboratory capacity in developing countries. On the other hand, detrimental effects emerge from drug supply interruptions within donor-funded programs.[83] Such examples illustrate the treacherous landscape against which patterns of resistance are rapidly evolving. Donors can and must do much more to systematically prevent resistance across all diseases.

The private sector—and specifically large pharmaceutical firms—have exhibited inconsistent leadership in protecting the drugs that they develop and manufacture. Much industry effort has

been targeted recently at counterfeiting, an increasingly pervasive and dangerous problem. Distinctive pills and hard-to-copy packaging are among the devices employed by companies. In addition, some companies have invested in tracking the efficacy of their products, as GlaxoSmithKline did for a decade through the Alexander Project.[84] With respect to leadership on drug research and development (R&D), few large companies remain significantly engaged in anti-infectives R&D, and those that are tend to focus on new drugs (e.g. for HIV or TB) rather than on diagnostics or other innovations that could help prolong drug efficacy. Where large companies are interested in this field of research, they often form partnerships with smaller bioscience companies that have made promising discoveries.

Lastly, regional leadership and collaboration are essential for tackling drug resistance as a cross-border concern. To date, most regional initiatives have had a regulatory thrust, and have struggled to develop momentum. Exceptions are the European Medicines Agency (EMEA) and the Pan American Network on Drug Regulatory Harmonization which are effective multicountry partnerships that cover a wide range of regulatory functions, including drug safety and efficacy. Regional drug regulatory networks have been established in West and East Africa, and Central and South Asia, with the intention of collaborating on quality, safety, and efficacy of pharmaceutical products, and increase communication among member countries on these matters.[*] As yet, however, the benefits of sustained collective action against drug resistance have not emerged from the various regional regulatory networks.

[*] The ECO (Economic Cooperation Organization) Drug Regulatory Authority Network was created in 2007, http://www.ecosecretariat.org/ftproot/Press_Rls/2007/1_HLDrug.htm.

The existing information base

The combined efforts of the small-scale and disease-specific programs and networks referred to above offer a woefully piecemeal picture of global drug resistance. The lack of systematic data on drug resistance trends at a country or even regional level, creates a chicken-and-egg problem. Insufficient awareness stemming from poor evidence makes drug resistance a low priority for donors and governments. Low levels of funding and political priority prevent assembling the evidence to demonstrate the extent of the health threat that resistance creates.

Three basic types of data are needed to identify, track, and manage the emergence and spread of drug resistance:

- Scientific data (e.g. molecular information), which can help us to understand how pathogens are mutating to resist different drugs
- Population data (e.g. epidemiological data), such as that generated through routine surveys and through public health surveillance systems, which can help us understand where and to what extent drug resistance is emerging and spreading
- System data (e.g. drug use information and cost data), which can help us understand some of the reasons why drug resistance is emerging and spreading

A number of disease-specific global databases hold scientific data related to drug resistance (e.g. molecular and genotypic information). Examples include the Stanford University HIV Drug Resistance Database, the International TB Genotype Database, and WHO TB Specimen and Strain Banks. Such databases are generally managed by small expert teams and are often housed by academic or research institutions. Very few are sustainably financed. Indeed, several databases have folded in recent years due to a lack of funds. Examples include the ARInfoBank developed by the WHO to capture data on antimicrobial resistance across diseases and the Los Alamos HIV Drug Resistance Database. This high degree of vulnerability in the scientific

knowledge base presents a significant risk to efforts to fight the emergence and spread of drug resistance.

Drug resistance data related to different populations are, not surprisingly, much more likely to be collected and analyzed in high-income countries. Both the United States and Europe (through their CDCs) have reliable public health laboratory and surveillance systems that routinely test for drug susceptibility and record the results, sharing information locally, nationally and regionally in an effort to detect and manage risks to public health. Some middle-income countries are investing in similar systems. A regional example is the Asian Network for Surveillance of Resistance Pathogens (ANSORP).[85]

In low-income countries the weaknesses in laboratory capacity highlighted previously mean that even basic data are not captured and that drug-susceptibility testing (DST) is rarely carried out. Some technical assistance is now available to help laboratories in resource-constrained settings to undertake DST using basic microbiological techniques and to record the results in ways that aid effective patient care and help monitor drug resistance trends. Indeed, WHONET has been doing this for more than two decades and has developed simple software for laboratories to download and deploy,[86] but the oversight and capacity-building it can offer is limited by its own severe resource constraints. Fortunately, a number of general laboratory strengthening initiatives have been launched in recent years. These include the Global Laboratory Initiative (instigated by the global TB community but likely to work more broadly) and the WHO/AFRO laboratory accreditation scheme supported by a range of U.S. technical agencies.[87] It is possible, therefore, that DST capacity will increase and this could lead to better drug resistance data collection and analysis. Meanwhile, some of the global health partnerships supported by donors, foundations, and multilateral agencies—such as Stop TB and Roll Back Malaria—collect the limited data that are available from low-income countries and map changing patterns of drug resistance as best they can.

New players in health-related surveillance could play a role in generating population data related to drug resistance. These include companies with informatics capability wishing to transfer technology or apply their learning to developing-country settings. For example, InSTEDD has a new disease surveillance initiative that could be adapted to gather resistance information.[*] It monitors many information streams for warning signs via a browser, and then helps gather teams together to undertake analysis and collaborative planning. Another relevant mechanism is ProMed, a relatively informal global electronic reporting system for emerging infectious disease outbreaks, which draws on information shared by email and through health discussion boards. ProMed is also working with HealthMap—a map-based disease-alert platform.[†] Several of these tools already capture limited drug resistance information by default. There is benefit in harnessing this potential more proactively, as such tools generate real-time data and the platforms already exist. With limited additional investment they could be used to fill a gap in our knowledge while more substantive, local surveillance capacity is built.

Tracking the use of specific drugs in localities would be a useful step toward identifying resistance hotpots or emergence zones. The availability of data on health services and pharmaceutical supply chains in developing countries has improved in recent years, with increased financing and technical assistance to build health and logistics management information systems. However, detailed drug use data have not yet become available through these systems. Developing countries that have social or community health-insurance schemes are better placed than others to accrue drug prescription and reimbursement data. In addition, some private data collection agencies such as IMS routinely collect information on drug sales in several Latin American, Asian, and African markets. New publicly supported global initiatives also work to improve data collection and sharing, such as the Medicines Transparency Alliance (MeTA), the International Network for the Rational Use of Drugs (INRUD), and the emerging

[*] See http://instedd.org/. InSTEDD's work is supported by Google.org.
[†] See http://www.promedmail.org and http://www.healthmap.org. This collaboration is also supported by Google.org.

WHO Medicines Use Database. This is a rapidly evolving field and information resources are likely to be strengthened over the coming years.

It is not enough to generate good data, however. There is a need to ensure access to this information and to support its use—particularly beyond the scientific and research communities. In knowledge-management terms, there is an urgent need for those concerned with drug resistance to reach beyond their relatively closed "community of practice" to build a broader "community of interest." Currently, many drug resistance data are not presented in a format that can be used by nontechnical parties (e.g. global health donors, developing-country policymakers). In addition, local capacity in resource-constrained settings is often insufficient to translate data into context-specific guidelines and to disseminate relevant and timely information to local health-care providers and policymakers.

In summary, our understanding of how drug resistance is evolving and spreading across the developing world specifically, and across the world more broadly, depends on the efforts of a small group of dedicated researchers and technical experts who operate within significant resource constraints. These limited resources—both human and financial—are concentrated in the fields of HIV, TB, and malaria, with relatively little dedicated to drug-resistance surveillance in other areas (e.g. bacterial illness beyond TB). As a result, policymakers and practitioners must base their decisions on patchy drug resistance data or, in many cases, on no recent data at all.

Innovations to slow drug resistance

New attention is being paid to the drug resistance problem, particularly in the area of research needs. The Bill & Melinda Gates Foundation, the U.S. National Institutes of Health, and the UK Wellcome Trust have all expanded grant-making in the field of drug resistance.[*]

[*] At the Gates Foundation this includes the Grand Challenges Explorations program http://www.grandchallenges.org/explorations/Pages/GrantsAwarded.aspx., now in the second year of funding

In the upstream technology sphere targeting diseases of the developing world (DDW), this new attention to drug resistance is epitomized by the proliferation of product development partnerships (PDPs) in recent years. PDPs are donor-funded nonprofit organizations that bring together researchers from academia, government, and industry under a common management and funding framework, which enables different lines of research to be prioritized through a portfolio approach, increasing efficiency and productivity. Each PDP generally has its own specific focus, either on a particular disease or technology, or on a group of neglected diseases.[*] While most PDPs are too young to claim marketed products, they can boast populating once-negligible pipelines with exciting candidates. A few, however, can claim real results: the Drugs for Neglected Diseases Initiative (DNDi) partnered with Sanofi-Aventis and the Brazilian Government, respectively, to develop and launch two new fixed dose ACTs for malaria;[†] and the Foundation for Innovative New Diagnostics (FIND) has partnered with WHO and CDC to conduct lot test evaluations of dozens of marketed rapid malaria diagnostics to inform procurement agents and health systems about their quality.[‡]

In addition to the PDP models developed to address DDW, a growing number of collaborative research platforms are available, which allow innovators to share ideas, research outputs and other information over the internet (see Box 3). Thus, they allow for some degree of virtual collaboration. Some of these platforms are membership- or subscription-based, or otherwise operated behind closed doors. Some are geared towards the sharing of patented innovations,

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basic science discovery related to resistance, as well as later-stage development of alternatives to Artemisinin for malaria treatment. At NIH, this includes a broad portfolio of resistance-related basic science research, primarily in the HIV/AIDS field. At Wellcome Trust, relevant new initiatives include ….(check with Ted Bianco.)

[*] Examples of PDPs focused on DDW include the Malaria Medicines Venture (MMV), the Malaria Vaccine Initiative (MVI), Areas TB vaccine initiative, the Global Alliance for TB drug development (GATB), the International AIDS Vaccine Initiative (IAVI), the Foundation for Innovative Diagnostics (FIND), the International Partnership for Microbicides (IPM) and the Drugs for Neglected Diseases initiative (DNDi). The nonprofit pharmaceutical company One World Health has a similar focus.

[†] http://www.mmv.org/IMG/pdf/COARSUCAM_WHO_PREQUALIFICATION_ENG_161008.pdf; http://www.msf.org.au/resources/position-papers/position-paper/article/msf-welcomes-new-fixed-dose-combination-against-malaria-developed-through-a-partnership-between-dndi.html

[‡] http://www.finddiagnostics.org/media/press/090424.html

while others are open-source collaborations. The basic two-heads-are-better-than-one rationale behind these virtual platforms is that researchers working together to reach a common goal will be more efficient than those same researchers working individually. Additionally, as we will discuss, some initiatives focus on the end goal of tech transfer—facilitating the licensure of potential innovations from academia to the private sector (iBridge Network), while others provide specific software packages to further advance R&D efforts in the near term (Collaborative Drug Discovery).

Box 3. Examples of existing drug discovery technology sharing arrangements

There are a number of existing platforms that allow researchers to share information or collaborate more extensively during the drug discovery process, including the following:

- iBridge Network (www.ibridgenetwork.org) and the Massachusetts Technology Portal (www.masstechportal.org) are web-based platforms, specific to groups of academic research institutions, that facilitate the sharing of information about research and recent innovations that have potential to make it out of the lab for commercialization.
- Collaborative Drug Discovery (CDD) (www.collaborativedrug.com) is a subscription-based for-profit platform that allows researchers to store and selectively share research data such as bioassays and chemical structures. It has recently been opened to noncommercial uses (e.g. to TB researchers supported by Gates Foundation financing, and to InnoCentive solvers).*
- Open Source Drug Discovery (OSDD) (www.osdd.net) is an open-source R&D platform focused on neglected diseases. Initially funded by the Government of India and hosted by its Council on Scientific and Industrial Research, OSDD now has a range of participants (academic, nonprofit, and corporate). It "aims to provide a platform for knowledge sharing

* See CDD and InnoCentive October 1, 2008, press release at www.collaborativedrug.com/blog/news/files/2008/10/cdd-innocentive-press-release.pdf

and collaborative research leading to identification of novel drug targets" and is initially focused on TB.

- GlaxoSmithKline's (GSK) "intellectual property pool for neglected tropical diseases in least developed countries" aims to enhance R&D related to 16 different conditions by facilitating access to GSK patent filings and expertise in small molecule pharmaceuticals.*
- Managed openings of pharmaceutical company compound libraries, usually for limited searching related to a specific disease (e.g. Pfizer's arrangement with WHO/TDR to allow screening of compounds for parasitic diseases,† Merck and Eli Lilly's collaboration to amass compounds for TB-related screening by the nonprofit Infectious Disease Research Institute).[88]

The current resistance-inducing behavioral landscape

Section III described how drug prescribers and dispensers make critical decisions on the basis of poor information or improper incentives. They also influence patient behaviors around drug use. There is perhaps no greater opportunity for reducing drug resistance than educating pharmacists and drug sellers in appropriate prescription and nonprescription medicines use given these players' potential role in changing consumer practice.[89]

However, current global efforts to encourage resistance-reducing prescribing and dispensing behavior are inadequate. For example, health professionals receive little, if any, systematic training in drug resistance. Neither core curricula nor continuing professional development (CPD) education of health professionals (doctors, nurses, pharmacists, laboratory workers) incorporate the development and prevention of drug resistance, including behavioral issues around rational drug use. Additionally, despite a rapidly changing drug and resistance

* See http://www.gsk.com/research/patent-pool.htm for more detail on this interesting new corporate approach.
† See http://www.ifpma.org/issues/index.php?id=247 for more detail.

environment, experienced developing-country prescribers rarely have opportunities to update their knowledge about new treatment options. Finally, prescriber sometimes receive direct rewards in the form of compensation for selling a higher volume of drugs.

Continuing education courses on rational drug use in developing countries are offered through international nonprofit agencies (such APUA, INRUD), universities (such as Harvard), contracting agencies (such as USAID-funded projects like Strengthening Pharmaceutical Services [SPS], housed within Management Sciences for Health [MSH]), in conjunction with national counterparts and often with support from and in collaboration with the WHO. Most such courses are funded through vertical program funds and are often disease-specific. Funding for participants is tight and their reach is limited.

Another reason that many qualified and registered pharmacists are currently not as engaged as they could be in combating resistance is that they often perform limited roles in practice, finding themselves limited to basic dispensing functions, with little time to educate or counsel patients. The International Pharmaceutical Federation (FIP) and others have argued that, if relieved of more routine roles, pharmacists could take on broader responsibilities—such as counseling and educating patients and liaising with colleagues from other health-care professions—to support the rational use of medicines.

Recent efforts to improve prescribing and dispensing behavior have targeted the informal sector, where a large proportion of anti-infectives are sold. A handful of developing-country initiatives implemented over the past decade reveal that incorporating informal providers into formal networks rather than relying on already-stretched enforcement mechanisms may be a more realistic behavior change approach and may have higher impact.[*] Evidence on the impact of these initiatives suggests that involving informal providers can, at least to some

[*] Three experiences in particular, in Ghana, Kenya, and Tanzania, highlight how franchising or accreditation might be used to encourage rational drug use. Such approaches have sought to improve access to affordable, quality-assured medicines, primarily in drug retail outlets in rural areas where registered pharmacies are scarce or absent. Typically, to become certified or join an accredited network, drug dispensers agree to undergo training, to maintain certain retail outlet standards, and to conform to other network requirements.

degree and under the right circumstances,[*] improve access to high-quality medicines and pharmaceutical services. In Tanzania, for example, creation of accredited drug dispensing outlets (ADDOs) has led to increased community access to essential drug products, to higher quality dispensing services, and to some improvements in appropriate drug use indicators.[90] Additionally there is evidence that ADDO implementation has improved community awareness of the importance of drug quality and treatment compliance and that consumers do associate ADDOs with higher-quality drugs and services.[91] The success of the ADDO program in Tanzania has prompted the Bill & Melinda Gates Foundation to recently award funding to increase involvement of private drug sellers in East Africa. This East African Drug Seller Initiative (EADSI) seeks to create a model for scaling-up private-sector medicine-dispenser efforts that will ultimately become self-sustainable.

Targeting provider prescribing and dispensing behavior may have more impact when accompanied by interventions that also address individual or community consumer behavior.[†] One noteworthy example that does not involve accreditation is an intervention to improve antimalarial use in Kenya. Skill-based workshop training of shopkeepers in rural Kifili led to a significant increase in the percentage of medicine sellers giving appropriate drug dosages (from 5% to 30%.)[92] Training was accompanied by provision of job aids, ongoing monitoring and community behavior change efforts (information outreach activities).[93] Another example from Kenya (Bungoma district) began with peer-education (wholesalers to retailers) as the core focus, but later added a neighbor-to-neighbor component, which sought to increase knowledge about malaria among caregivers as well as increase demand for antimalarials.[94]

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[*] The limited experience to date suggests that several factors are critical to success. See E. Rutta et al., "Creating a New Class of Pharmaceutical Services Provider for Underserved Areas: The Tanzania Accredited Drug Dispensing Outlet Experience." *Progress in Community Health Partnerships: Research, Education, and Action* 3 no. 2 (Summer 2009).

[†] Evidence has shown that multifaceted and coordinated interventions have a larger impact on modifying prescribing behavior than do single-pronged interventions. See summaries of evidence from the 2nd International Conference on Improving Use of Medicines (ICIUM) at http://www.icium.org/icium2004/

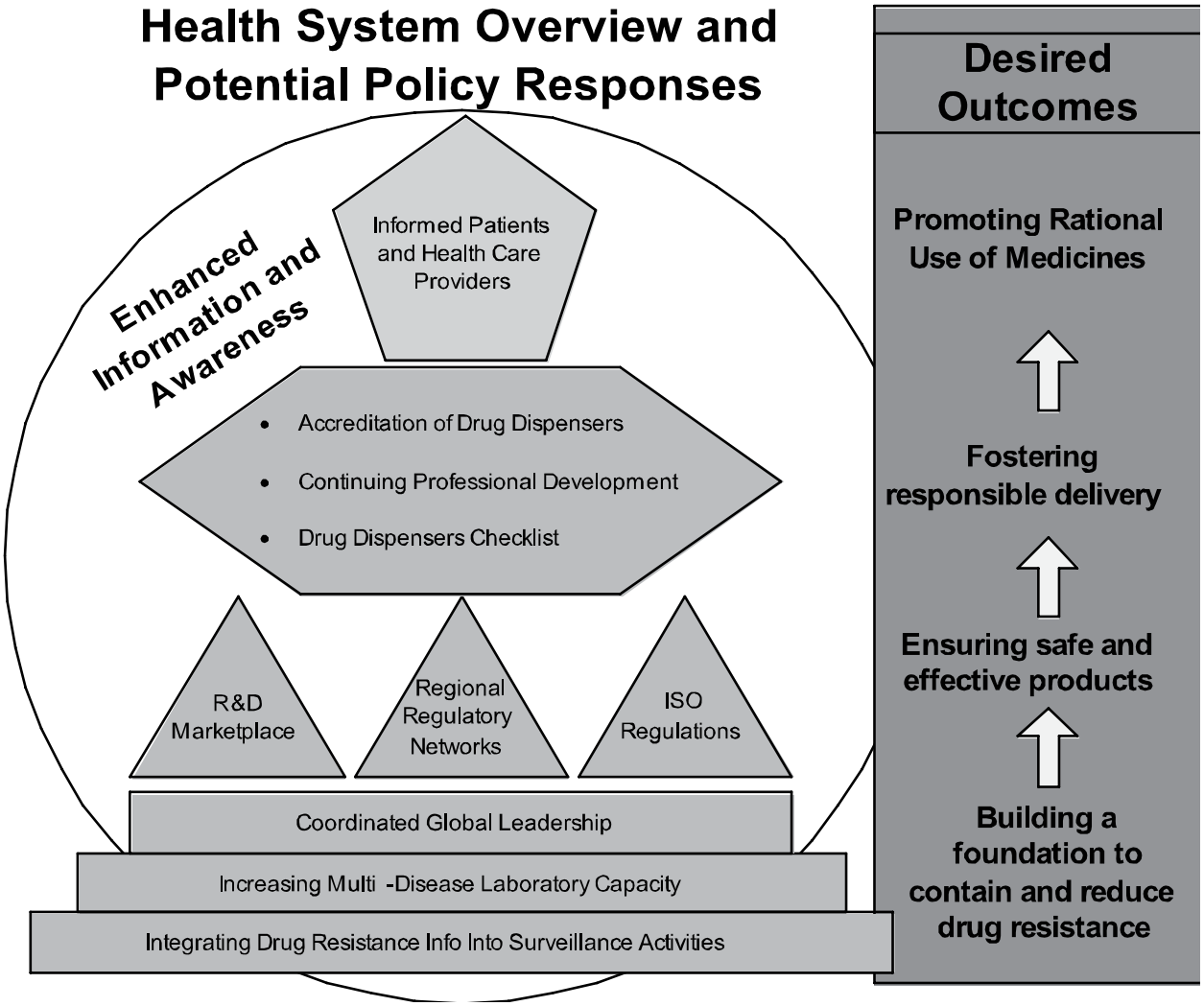
In sum, a number of disease- or country-specific initiatives have been implemented over the past decade with the (at least partial) goal of improving prescribing and dispensing behavior. Several efforts seem to have successfully improved dispensing practice in informal settings—at least over the short term.[95] These efforts have often been multifaceted, involving components such as regulatory enforcement, peer interaction, outreach, and incentives.[96] Scale-up of such approaches within a given country or region clearly requires considerable medium- to long-term financial, managerial, and political support to ensure success.

V. A Set of Practical Steps to Fight Drug Resistance

The CGD Drug Resistance Working Group has identified a set of essential actions that, taken together, will go far to contain and reduce drug resistance globally. Each has merit individually, but their strength in attacking the problem lies in taking a unified approach to identify, suppress, and respond to resistance, with both public-sector and private-sector energy.

The recommendations can be grouped into three categories: information, tools, and leadership. Figure 5 shows how they work together as an integrated and comprehensive approach to drug resistance.

Figure 5. A System of Recommendations to Tackle Global Drug Resistance



The ultimate objective of a coordinated approach is to create better behavior among health-care providers and consumers so that their decisions reflect society's true interest in maintaining effective and sustainable drug access to treat infectious disease. Therefore, patients and providers are at the pinnacle of the comprehensive approach. Taking a small set of proven actions to change the incentives of health-care providers can encourage appropriate dispensing. Realigning regulatory and private-sector incentives can help ensure that technology development and product safety and efficacy are given greater priority. Both emphasize better use of information and enhanced opportunities for collective behavior that can achieve mutually beneficial results. All the steps to realign incentives must be built upon a foundation of better drug-resistance knowledge and leadership. Such steps are described with a specific recommendation below.

Gather Better Information and Use It

The shared resource of drug efficacy cannot be protected without informed collective action. A first step is developing a common view of the problem—a shared understanding of when, where, and how drug resistance is emerging and spreading. This suggests that the information resources central to managing drug resistance should be treated as "global public goods," with all societies contributing to their maintenance and able to access and benefit from them. This includes, most critically, drug-resistance surveillance data and information about the quality of drugs circulating in the pharmaceutical market.

Better information will feed directly into public- and private-sector efforts to protect drug quality. These efforts will be far more effective if they draw strength from common motivations. With the appropriate institutional mechanisms, cooperation can replace competition or willful neglect. National capacity to monitor and enforce drug quality standards should be strengthened and reinforced through a collective response. In addition, the private sector should use its marketing and supply-chain monitoring capabilities to establish and

enforce industry standards for drug quality and safety. We propose three actions to accomplish these goals, starting with a more systematic way to gather and share resistance information.

1. **Increase drug resistance surveillance**

   We recommend that the global health community establish a multidisease surveillance system that can track the emergence and spread of drug-resistant strains of disease, and develop accessible and meaningful data sharing systems for multiple purposes, including for policymakers and global funders.

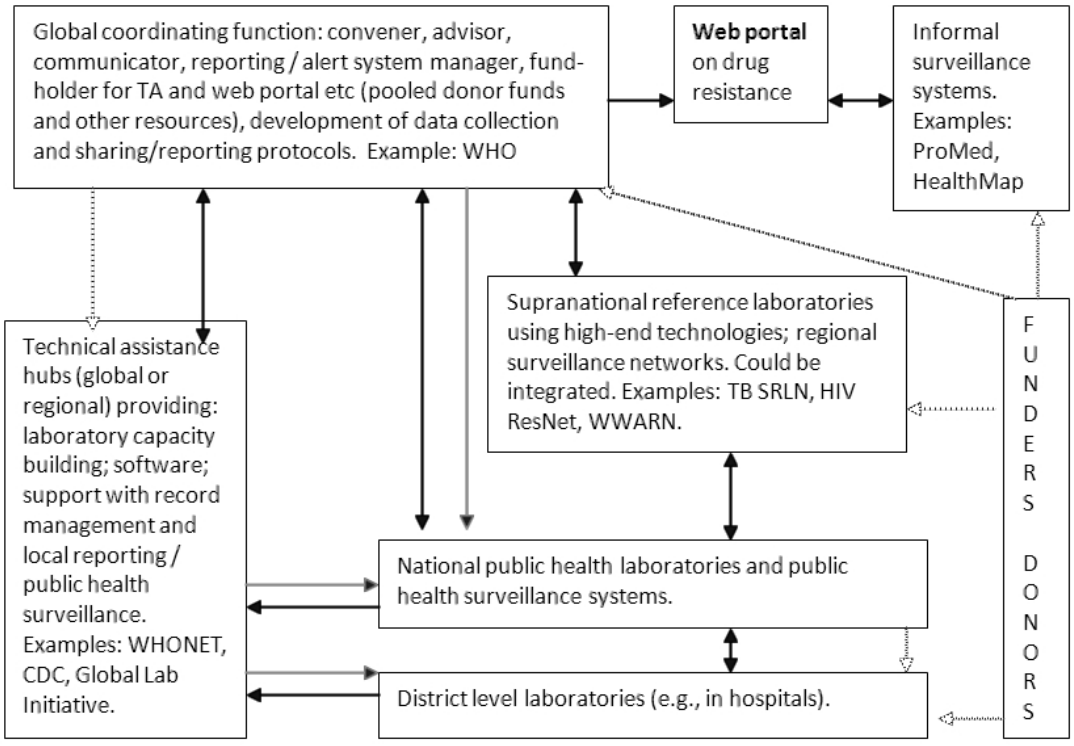
Key points to consider in implementing this recommendation:

- New protocols for **information sharing** will need to be developed. It will also be important to ensure that both public and private actors are undertaking coherent and consistent approaches to drug-susceptibility testing and related data collection.
- There is an urgent need for **investment** in related human and physical capital, particularly with respect to laboratory capacity.
- Investments should develop and strengthen the capacity to undertake **routine drug resistance surveillance across diseases**—through basic microbiological laboratory services at national and district levels—as appropriate given the country context—and integrating this with broader public health surveillance systems.[*]
- National institutions should better utilize supranational reference laboratories, where more advanced molecular technologies are increasingly deployed. Existing supranational laboratories focused on single diseases would need to be enhanced and integrated to provide a **cross-disease network** with increased capacity.

[*] WHONET is well placed to provide technical assistance in this area, as it has developed freely downloadable software (available in at least 15 languages) to help technicians in resource-constrained laboratories to record and analyze patient data in order to track drug use and patterns of resistance. This supports effective patient care, as well as yielding useful trend data to support ongoing drug resistance surveillance. Even with very limited resources, WHONET provides both remote and in situ technical assistance to laboratories using the software, to help them deploy it effectively. With more significant and sustained resourcing, the WHONET team could expand technical assistance and support efforts to analyze and aggregate data for the purpose of broader surveillance.

- Strengthened cross-disease drug resistance surveillance could be shared in a format suitable for public use through a **web-based information portal**. This would enable resistance data from multiple sources to be presented in a range of compelling formats, to be usable by policymakers as well as health professionals.

The diagram below shows how a global cross-disease drug-resistance surveillance system would draw on the comparative advantages and specific expertise of existing players. Many of the needed tools and technical functions already exist within designated health organizations. The primary innovation would be to develop and implement new protocols for the collection, recording and sharing of drug resistance data. Some of the implementing organizations mentioned would need additional financial and human resources to operate at the scale demanded by such a system. The drug resistance web portal would vastly enhance the global knowledge-base on resistance, and increase the ability of donors, technical agencies, and national governments to evaluate the effectiveness of drug resistance control measures.



KEY: Black arrows = information/data flow; Gray arrows = technical assistance; Dotted arrows = funding.

Making drug resistance surveillance routine across all societies and for all significant infectious diseases would have major benefits. Timely information about pathogen susceptibility will enable better management of patients and aid infection control in clinical settings. Aggregating the data to population level will make possible more informed policymaking and action in the following areas:

- National level: drug policy, essential-medicines lists, standard treatment guidelines, procurement strategies, resource allocation, health professional curricula and training
- Regional level: harmonized regulations, cross-border responses
- Global level: donor resource allocation, global alert and response systems, R&D agenda setting, normative and standard setting, WHO recommendations and guidelines, procurement by global health initiatives

The key is to develop a system now that can be sustained over the long term as new technologies come on line, and which eventually can be translated to lower levels in the system (i.e., closer to the point of care, where they can inform the management of drug resistant disease as well as simply detecting it).

2. **Support national regulators to improve drug quality surveillance**
   We propose that national and international support be provided to create new regional networks of drug regulators and encourage existing ones to address the problem of drug resistance and develop shared incentives to protect drug efficacy. A well-functioning, mutually-supportive regulatory network will enable individual NDRAs to achieve greater effectiveness and efficiency.[*]

Because they share many epidemiological and market conditions, countries in a region can fortify one another's efforts to maintain a quality drug supply. Regional networks formalize the

[*] Successful regional networks may eventually lead to more broadly harmonized regulatory processes as exemplified by the European Medicines Agency (EMEA.) This recommendation is focused on building regional capacities for drug quality assurance and monitoring.

interdependency that exists among adjacent countries by enhancing the incentive for collective action, and reducing the incentives for "free riding" on other's efforts. Some countries already engage in regional regulatory cooperation and need only sustained financial support to implement collective efforts against drug resistance. An example is West African Drug Regulatory Authority Network (WADRAN), affiliated with ECOWAS in West Africa.

How might this work?

- Regional activities and responsibilities should include
    - drug resistance surveillance cooperation;
    - human-resource strengthening, particularly within regulatory agencies;
    - harmonizing quality-assurance processes and sharing information about substandard products;
    - aligning national drug policies and standard treatment guidelines.
- Specific terms of reference, mission statements, and staffing should be determined by the distinct needs of the regional networks.
- Donor priority should be given to establishment and strengthening of regional networks in Africa.[*]
- Because the benefits of effective regional management of drug resistance would be widespread—beyond the specific countries involved—support for the networks should be sought from international sources, as well as from the governments involved.

People rely first and foremost on national regulatory agencies to inform and protect them from unsafe and poor-quality drugs. National authorities in many countries are severely challenged to keep up with the demands of ensuring drug quality. If underresourced NDRAs were relieved

[*] DFID, the Gates Foundation, and the Clinton HIV/AIDS Initiative are working with the WHO to support a continental harmonization initiative in Africa; other donors and agencies are supporting regional efforst of the Southern African Development Community. However, these efforts do not focus much on sharing information about drug quality or drug-resistance data. The Medicines Transparency Alliance (MeTA) does support the disclosure and dissemination of data on drug quality—albeit for just seven countries currently.

of some of their upstream responsibilities—possibly with some form of financial compensation— they could focus their scarce resources on downstream regulation of the domestic pharmaceutical market, strengthening areas such as post-marketing surveillance (including testing drug quality at sentinel sites), which could reduce drug resistance.

Existing regional networks can and do vary according to the needs and challenges of the member countries, and need to have institutions and rules that guide the relationships and accommodate the regional conditions. The approach has been successful where drug regulation functions well, and has worked less well in some parts of Africa and Asia where drug regulation is spotty. The degree to which national drug regulators work together varies substantially across regions with the weakest links being where the need is greatest: in sub-Saharan Africa. It is admittedly a complex task to design regional programs that balance contributions and needs across countries of disparate capacity and policy authority. This may explain the World Bank's recent finding that regional programs account for less than 3 percent of all international development support.[97] The World Bank study emphasizes the potential for regional programs to have significant impact, especially when lessons from earlier experiences are applied. The need for and contributions of regional efforts will likely increase, and protecting drug efficacy is a compelling application.

3. **Encourage the Drug Industry to Monitor Drug Quality**

   We propose that drug manufacturers work through their industry associations to develop and implement a set of uniform global standards and procedures to measure and monitor drug resistance, and to validate the measures they take to reduce threats to drug quality and assure appropriate drug use. These standards would include industry incentives to demonstrate and achieve compliance.

Drug manufacturers share responsibility with regulatory authorities for providing safe and high-quality drugs and for tracking their continued effectiveness. As with the efforts of regulators, there is greater emphasis on safety than on quality, through pharmacovigilence and tracking

adverse drug reactions. Drug manufacturers currently have mixed incentives to expose and address resistance to their products.[*] Drug manufacturers can make their drug testing and surveillance more routine and transparent and decrease the time between detecting problems and fixing them.

A set of industry standards to reduce the development of drug resistance by ensuring rigorous and transparent post-marketing quality monitoring, testing, and improvement would reduce the circulation of poor-quality drugs, restore confidence in the quality of the global drug supply, and reduce the burden on regulatory agencies. It would also give responsible pharmaceutical companies a market advantage over competitors that do not meet standards, it would and exert pressure on the latter to improve their efforts to improve quality.

One internationally recognized and validated means to achieve industrial quality standards is through the International Organization for Standardization (ISO.) The ISO develops standards and certifies compliance following an industry-wide, voluntary, consensus process that defines the technical scope of future standards. While there are already international standards for pharmaceutical manufacturing processes through the WHO's Good Manufacturing Process (GMP) program, no international standards or monitoring procedures exist for post-marketing assurance of drug quality. Even local manufacturers in developing countries that do not meet GMP standards have incentive to demonstrate the high quality of their products to their main wholesale and retail purchasers in the countries they come from.[†]

The information conveyed by an ISO certification could induce drug purchasers to be more selective. An ISO certification of quality standards could allow consumers to quickly differentiate those products they can trust from those they cannot. In addition, the quality

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[*] See Yadav, "Countering Drug Resistance in the Developing World: An Assessment of Incentives across the Value Chain and Recommendations for Policy Interventions," CGD Working Paper 183 (Washington, D.C: Center for Global Development, 2009).
[†] ibid.

certification could become an important signal to inform the buying decisions of major purchasers of drugs for developing countries—both national governments and donors.

The ISO is not the only way to achieve the proposed standards and procedures, but has some merits. It exists to maintain quality in industrial processes, and has a careful and inclusive process of developing certification procedures. It relies on industry involvement and expertise, and thus is credible to the industry and adaptable to changing technologies and conditions. Developing new ISO standards is a long and arduous process, but there are some existing standards that might be adapted to improving global drug quality. A set of management standards for the health industry already exists to proactively prevent problems and provide ways to detect and correct problems in processes.[*] This might be a useful place to begin designing the processes needed to reduce errors and omissions that lead to resistance in the post-marketing supply chain for drugs. With sufficient enthusiasm from the pharmaceutical industry, it might also be an opportunity to better align industry interests and actions with government and public interests in maintaining a quality drug supply.

Develop better technology and protect it better to improve rational use of drugs

There are promising advances in R&D targeting neglected diseases and populations, yet drug resistance is still relegated to the outer margins of disease-specific initiatives. There is no PDP and no technology sharing arrangement specifically focused on drug resistance. Further, insufficient knowledge and inappropriate use of the technology we do have—both drugs and diagnostics—puts into question the value and longevity of investments to protect them from resistance. We offer three steps that would stimulate new resistance-specific technology development and improve appropriate use of that technology.

[*] Called ISO 9001:2000 this certification is used to improve systems within health care.

1. **We recommend the creation of a web-based marketplace for the sharing of resistance-specific research and technological innovations across diseases. This facility would aim to create partnerships and lower transactions costs for all potential collaborators. By aiding early-stage scientists to partner together and learn from one another, the marketplace could ultimately catalyze this research, which would, in turn, accelerate the development of these technologies.**

Examples of resistance-specific research and technologies that such a marketplace would focus on include, but are not limited to, new classes of therapeutics, point-of-care (POC) diagnostics, rapid drug-susceptibility tests (DSTs), improved drug-delivery methods, efflux pump inhibitors, and fixed-dose combinations (FDCs). In the long term, these technologies have the potential to become both new products to defend against evolving microbes (e.g., new classes of therapeutics, FDCs), and new tools to facilitate their more rational use (e.g., improved POC diagnostics, rapid DSTs and drug delivery methods).

The incentive structure of such a drug resistance marketplace would follow the precedent of many of those that have come before it. On the "supply" side (those entities contributing and providing inputs), the marketplace would act as a gateway for early-stage researchers to virtually share their work in, and knowledge of, resistance-relevant technologies with others, as a way to advance development through collaboration. Initially, we foresee these contributors to be mainly from public-sector labs—academic and government—and nonprofit research organizations. With less motive on profit and more on having their innovations known, so as to help propel them out of the lab and across the tech-transfer "valley of death," these players have traditionally been the first adopters of these types of initiatives. Building the marketplace this way enables it to get off the ground without running into the more traditional intellectual property issues that arise when dealing with companies opening up their compound libraries. When activity increases enough to achieve a critical mass, smaller companies, many of which have recently been spun out of academic labs themselves, then follow. Once a marketplace proves itself to be secure in protecting patents and trade secrets, and companies can reliably be

selective with whom they wish to collaborate, industry buy-in will be more pronounced, as has been the case with CDD. Similar to CDD, we foresee the marketplace needing a permanent host, perhaps a nonprofit organization, to facilitate partnerships and oversee the day-to-day operations by providing guidance on legal, business and contractual issues that may arise.

On the "demand" side, (those entities wishing to find new technologies to privately develop them), later-stage biopharmaceutical companies, funders, and venture capitalists could use the marketplace as a one-stop-shop to significantly decrease the transactions costs of evaluating those innovations or discoveries that may be worthy to in-license, fund, or otherwise partner with. This incentive for reduced transactions costs can already be seen in recent industry activities. For example, in June 2009, Eli Lilly & Company announced the launch of their Phenotypic Drug Discovery initiative (PD^2).[*] It is exactly the same type of marketplace we are calling for, except that it is focusing on adding to Lilly's profitable pipeline diseases—cancer, Alzheimer's, osteoporosis, and diabetes—and of course Lilly retains control of the whole process, with the first rights to a licensing deal. While these company-led initiatives may proliferate for profitable platforms, the resistance marketplace will remain relevant for resistance-specific technologies.

In addition to incentives being aligned for both suppliers and demanders to participate in such a marketplace, encouraging evidence from the Gates Foundation's Grand Challenges Explorations initiative suggests there is a significant pent-up supply of resistance-relevant research . Under the initiative's category of "Create Drugs and Delivery Systems to Limit Drug Resistance," the Foundation received over 1,200 applications in its first two grant rounds, of which they were able to fund 35.[†] That leaves hundreds of researchers working in this area in need of funding to advance their ideas, discoveries and innovations.

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[*] http://newsroom.lilly.com/releasedetail.cfm?ReleaseID=389589

[†] http://www.grandchallenges.org/Explorations/Pages/Introduction.aspx and private conversations with Gates Foundation employees

This trend towards collaborative R&D, while promising for DDW, is also increasingly necessary for biopharmaceutical companies in all disease areas. In recent years, many of the big drug makers have significantly retreated from early-stage discovery work, slashing research staff to focus on later stage development and clinical trials. As a result, these research scientists who are experts in drug discovery have dispersed either into the hundreds of smaller pharmaceutical and biotech companies that have emerged to fill this gap, or into other academic, nonprofit, or government labs. To fill their pipelines, the big drug makers are increasingly in-licensing candidates from these smaller entities: hence, the need for initiatives such as Eli Lilly's PD^2.

Whether due to necessity or improved technological capacity, the trends in recent years have been towards increasing information sharing and collaboration in the product development arena. Creating a similar type of virtual marketplace for resistance-relevant technologies has the potential to catalyze the R&D efforts for these much needed innovations by promoting collaborations and decreasing transactions costs. By accelerating the development of these products (new classes of therapeutics, POC diagnostics, rapid DSTs, improved drug-delivery methods, and FDCs) in the long term, both fronts—the lack of new products in the pipeline to defend against ever-evolving microbes, and the misuse of those products that we do have—can be addressed to contain and reduce drug resistance.

2. **To encourage more appropriate drug dispensing and patient education about appropriate drug use, we propose systematic resistance-specific training for pharmacy workers. Implementation of a sustained and global-level drug-resistance education effort specifically targeting pharmacists and pharmacy assistants will improve drug prescribing, dispensing, and use.**

Relevant global health actors (such as the International Pharmaceutical Federation [FIP] and the World Health Organization [WHO]) should lead development and implementation of drug-resistance-specific curricula. Generation of local and regional drug-resistance information is a

critical component of education efforts and to informing country-level policy. Therefore, linking the improvements in global resistance surveillance proposed above to local resistance information through dispensers is a necessary step to achieving more appropriate drug use. Evidence from developed-country research clearly shows that interactive continuing professional development (CPD) can result in changes in professional practice and, at times, improve health outcomes.[98]

Drug-resistance-specific curricula should cover multiple diseases. Modules would cover current trends in the emergence and spread of drug resistance (globally, regionally, and locally), give examples of changes in drug policies or standard treatment guidelines as a result of increased knowledge about resistance patters, recommended actions to protect drug efficacy, survey behavioral challenges to rational drug use and how these might be overcome, and proffer advice to give to patients.

In addition to core curricula, drug-resistance-specific CPD modules based on local resistance data for pharmacists are needed to guide evidence-based prescribing and dispensing decisions as disease epidemiology and prescribing practices change. CPD for lower-level pharmacy workers could also focus on training in routine dispensing practice, thus enabling more qualified and registered pharmacists to take on broader responsibilities—such as counseling patients on adherence and educating and connecting with colleagues from other health-care professions—to support the rational use of medicines.

3. **To effectively encourage more rational dispensing of quality drugs, we propose scaling up the accreditation of dispensers. Accreditation would target informal dispensers and provide incentives (financial or otherwise) to modify dispensing behavior.** [*] **Scale-**

[*] There clearly is potential to influence appropriate prescribing in accredited units using financial incentives; for example, dispensers could receive a small bonus when they dispense an entire course of medicine. Alternatively (or in addition), regulators could penalize a dispenser when an incomplete course is dispensed. Where third-party payers play a considerable role in drug purchasing (or reimbursement), there is potential to explore ways to

up of effective certification programs should increase dispensers' knowledge about drug resistance. Additionally, it would create opportunities for quality product differentiation by consumers as they begin to associate certified "brands" of drug distributors with higher quality drugs and service.

Evidence suggests that multifaceted interventions* that include components such as regulatory enforcement, peer interaction, outreach, and incentives are the most effective at changing behavior and achieving more rational drug use.[99] Hence, dispenser accreditation schemes are likely to have more impact when accompanied by interventions that also address individual or community consumer behavior.

As a first step to inform an evidence-based scale-up of approaches to engage informal dispensers, funding should be secured to commission research to identify the set of minimum basic services and standards that would make up an accreditable core drug-provision model that could become self-sustainable over the short- to medium-term. The costs of implementing such a package would be estimated as part of this research. Simultaneously, efforts should be made to sensitize funders (external donors and national governments) to the fact that introduction of an accreditation model within a country will require acceptance of and commitment to ongoing expenditure for an extended period of time.

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incentivize these payer groups (insurance, government, employers) to encourage more rational use of drugs. For example, there is evidence from Ghana and South Africa that patients are being switched from 1st to 2nd line ART for no clear reason. This has strong health, resistance and cost implications. One idea would be to incentivize, monitor and reward appropriate withholding of 2nd line treatment and appropriate referral.

* One example of this, which does not involve accreditation, but which is noteworthy given its impact, is an intervention to improve antimalarial use in Kenya. Skill-based workshop training of shopkeepers in rural Kifili, which was accompanied by provision of job aids, ongoing monitoring and community behavior change efforts (information outreach activities) led to a significant increase in the percentage of medicine sellers giving appropriate drug dosages (from 5% to 30%) (VM Marsh et al., "Improving Malaria Home Treatment by Training Drug Retailers in Rural Kenya." *Trop Med Int Health* 9:451–460; C. Goodman et al., "Medicine Sellers and Malaria Treatment in sub-Saharan Africa: What Do They Do and How Can Their Practice Be Improved?" *Am. J. Trop. Med. Hyg.*, 77 Suppl. 6 [2007]: 203–218.)

Development and training in the use of drug-resistance specific guidance tools, such a drug-dispenser checklist could also help in the fight to preserve currently effective drugs. A simple checklist device for both formal and informal drug dispensers (particularly those with less formal education or training) can guide how drugs are selected, stored, and distributed. Such drug-dispenser checklists could be a core component of CPD efforts. If tied to measurable behavior which can be monitored, drug-dispenser checklists can also be an effective tool to improve dispensing behavior as part of an accreditation process.

Given that FIP has prior (positive yet limited) checklist experience, national chapters of the FIP could be logical leaders in development and implementation of a simple generic drug-dispenser's checklist—in essence, a list of practical guidelines to prevent the emergence and spread of drug resistance. Once developed, this generic checklist would need to be customized to local conditions. It would also need to undergo periodic review, adapting to changing conditions, while aiming squarely to change society's knowledge and behavior about resistance. To achieve the desired impact, the consequences of poor performance on a checklist would need to be real, such as tying recertification of an accredited informal dispensing outlet to appropriate dispensing practice.

Secure Strong Global Leadership

What has been most absent in tackling global drug resistance is leadership at the international level. This leadership vacuum must be filled. But the complexity of the problem requires multiple actors to provide leadership, both individually and collectively. It has been too common for each of the key decision-makers in the drug-supply and -use spectrum to sidestep their responsibility to protect drug efficacy and put the blame for resistance elsewhere. These so-called villains have included: "poor regulation," "ignorant consumers," "greedy prescribers," "profit-oriented brand-name pharmaceutical companies," "drug counterfeiters," "biological mechanisms," and so on. In fact, resistance can be traced to each of these drivers, but it can't be resolved by fixing them individually.

- **We propose that global organizations convene an international drug-resistance and development conference (IDRDC)** in 2010 as an important milestone toward the recognition across disease and institutional communities that concerted action will achieve more than continued piecemeal efforts against resistance. The conference would set forth an international agenda for responding to drug resistance across multiple disease areas. It would galvanize those concerned about drug resistance to share information, create systematic and coordinated responses, and recognize that investments in drug resistance prevention and control are just as valuable as investments in drug development and access. The two go hand in hand.

- We propose that the WHO and its Member States take steps to **strengthen the International Health Regulations** in language and practice as they apply to drug resistance. As discussed previously, the most recent version of the International Health Regulations (IHR 2005) does include the need for countries to report certain cases of drug resistant disease to the WHO. However, references to drug resistance are nonspecific and hard to interpret, and it is not clear that reporting has been enhanced in practice. It has also been suggested that new measures be added to the IHR to protect drug efficacy, such as banning the production and use of antimalarial monotherapies.[100]

At a minimum, it would be helpful for the global health community (and the WHO specifically) to reiterate the relevance of the IHRs in the context of managing the emergence and spread of drug resistant pathogens. One way to do this would be through IHR guidance to countries. The WHO would then need to provide technical assistance to countries to help them comply with the IHR and use the guidance. As an additional step, the WHO could convene a technical working group to explore and agree on ways to enhance the IHR as a mechanism to mandate appropriate drug use and other actions to slow the emergence and spread of drug resistance.

Developing countries will only be able to comply with such measures if other forms of financial and technical support are provided to help them track, report, and respond to drug resistance. The IHR must therefore be strengthened in conjunction with the other actions recommended in this report.

Needed Research to Support a Global Response to Drug Resistance

Research is needed to quantify the full economic impacts of drug resistance within countries and globally. There are few studies on the economic costs of resistance and careful interpretation of existing studies is warranted. The working group acknowledges the caveats of poor data but believes that an assessment of the economic costs of resistance must be made available to global and national policymakers and donors. The literature is dominated by studies from developed countries and is disease- or drug-specific. Because costs in developing countries are vastly different, this report does not provide a full discussion of the existing literature. Therefore, we point out the limitations of prior economic studies of resistance and urge the World Bank and other global funders of drug treatment to support rigorous analysis of the social costs of drug resistance. In order to evaluate the results of recommendations we make above, information is needed to ascertain the costs of resistance and the benefits derived from protecting drug efficacy more rigorously.[*]

Research is needed to investigate the effects of the use of drugs as prophylaxis, specifically to

- track people involved in clinical trials for drug-based prophylaxis to monitor the long-term impacts of these technologies on the emergence and spread of drug resistance;

[*] Supported by the Gates Foundation, pilot studies have recently begun to collect and analyze economic data on anti-microbial resistance in a limited set of countries.

- assess the risks presented by the use of the same drugs for both prophylaxis and treatment, including across diseases.

The use of drugs as prophylaxis—that is, to prevent the transmission of disease or its development in an infected individual—is widespread across both the developed and developing world, and it encompasses a broad range of practices, from the casual use of antibiotic creams to limit infection in cuts and grazes to the use of emergency post-exposure prophylaxis with ARVs for women who have been raped. Another example is doxycycline, which is an antibiotic used to treat a range of conditions (e.g., sexually transmitted diseases, acute respiratory infections, and various gastrointestinal conditions) but is also used as an antimalarial prophylactic.

Concern has been expressed that drug-based prophylaxis—particularly for patients with compromised immune systems—could drive the emergence of resistant microbes. Prophylactic drug regimens will also become less effective as microbes that are resistant to them spread. On the other hand, if the use of prophylaxis prevents disease transmission, they may help limit the selection pressure for resistance. In short, the scientific evidence in relation to prophylaxis and drug resistance is thin, and the rules governing the emergence of resistance are not well understood.

As the risks to drug efficacy posed by prophylactic regimens differ according to the pathogen under consideration and the drug used, the only way to identify and mitigate such risks is through operational research and surveillance, and through evidence-based policy and practice. At a minimum, participants in prophylaxis clinical trials should be recruited into follow-up programs so that resistance-related risks can be effectively monitored over the long term. Maintaining a distinction between the drugs used for prophylaxis and those used for treatment would also be prudent, at least until a stronger evidence base has been developed.

Research is needed to quantify the scale and impact of antibiotic use in animals in developing countries, particularly across Africa. The relationship between the use of antibiotics in food animals and patterns of drug resistance in humans in developing countries is not well understood, and further investment is required to develop a useful knowledge-base. In industrialized nations, we arguably know enough already to necessitate action. However, comparatively scant research has been undertaken on the impact of agricultural and veterinary drug use on drug resistance in developing-country settings. Both data collection and analysis are needed.

A first step in any research program must be to ascertain the full extent of antibiotic use in food animals in developing countries across Africa, Asia, and Latin America. A systematic review of the literature documenting the presence of antibiotic-resistant microbes in animal feed, carcasses, and meat products in developing countries would also be immensely valuable. This area of research ought to be attractive to bilateral donors with a history in financing both agricultural and health research.

Conclusions

The evidence cited in this report indicates that drug resistance is a large and growing problem that contributes significantly to illness and death across the world. It has a particularly harsh impact on poor people in developing countries; it harms their ability to prosper and contribute to their societies and adversely affects their children's health and development. However, drug-resistant forms of disease emerge and spread in every society and affect us all. This is a global problem demanding a systematic global response.

Technical experts of all types have expressed deep concern over the existing levels of drug resistance and future implications, but these concerns have fallen on the deaf ears of global donors and policymakers. Drug resistance is fuelled by many different factors, and tackling it presents a complex challenge. However, there are things we can do collectively to slow its emergence and spread and to limit its impact.

This report highlights three urgently needed priority areas for investment:

- Better information about where and how drug resistance is emerging and spreading, particularly across developing countries
- Action to protect the drugs we use currently and those we will have in the future
- Strong global leadership to ensure an effective and well-coordinated response

Action must be taken in all countries, but developing countries will need targeted technical and financial support from the international community if they are to act effectively. The problem of drug resistance must be addressed with a long-term view and sustained financial and human resource commitments. Action is needed now.

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Notes

[1] Global Project on Anti-Tuberculosis Drug Resistance Surveillance. Anti-tuberculosis drug resistance in the world: report no. 4. Geneva, Switzerland: World Health Organization; 2008

[2] A vGottberg, K. Klugman, C Cohen, N Wolter, L de Gouveia, M du Plessis, R Mpembe, V Quan, A Whitelaw, R Hoffman, N Govender, S Meiring, AM Smith, S Shrag, for the Group for Enteric, Respiratory and Meningeal Disease Surveillance in South Africa (GERMS-SA). Emergence of levofloxacin-non-susceptible Streptococcus pneumoniae in children in South Africa: a cohort observational surveillance study. The Lancet Online. Published online March 24, 2008. and RJ Davidson, I Davis, BM Willey, K Rizg, S Bolotin, V Porter, J Polsky, N Daneman, A McGreer, P Yang, D Scolnik, R Rowsell, O Imas and MS Silverman. Antimalarial therapy selection for quinolone resistance among Escherichia coli in the absence of quinolone exposure, in tropical South America. PLoS ONE

[3] Prevention and Control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis, Report to the 62nd World Health Assembly, WHA62.15, May 2009, WHO, Geneva.

[4] Prevention and Control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis, Report to the 62nd World Health Assembly, WHA62.15, May 2009, WHO, Geneva; Borgdorff, M. and P. Small, Lancet, v. 373, May 30, 2009.

[5] http://www.stoptb.org/gdf/

[6] WHO, 2009, Medicines use in primary care in developing and transitional countries, Geneva.

[7] Alan D. Lopez, Stephen Begg, and Ed Bos, "Demographic and Epidemiological Characteristics of Major Regions, 1990—2001." 2006. Global Burden of Disease and Risk Factors,ed. , 17-44. New York: Oxford University Press. DOI: 10.1596/978-0-8213-6262-4/Chpt-2.

[8] Medicines use in primary care in developing and transitional countries: Fact Book, available at http://www.who.int/medicines/publications/who_emp_2009.3/en/index.html

[9] Walker B., S. Barrett, S. Polaskey, V. Gafaz, C. Folke, G Engstrom, F Ackerman, K Arrow, S Carpenter, K Chopra, G Daily, P Ehrlich, T Hughes, N Kautsky, S Levin, KG Moaler, J Shogren, J Vincent, T Xepapadeas, A de Zeeuw. 2009. "Looming Global-Scale Failures and Missing Institutions, Science, 325; 11 September, 1345-46.

[10] http://www.cmaj.ca/cgi/content/full/180/4/416#F119)

[11] http://www.pepfar.gov/about/c19388.htm, http://www.theglobalfund.org/en/distributionfunding/?lang=en, http://www.unitaid.eu/images/news/annual_report_2008_en.pdf).

[12] Laxminarayan, R., ed., Battling resistance to antibiotics and pesticides: An Economic Approach, RFF Press, 2002.

[13] WHO Report 2009: Global Tuberculosis Control Epidemiology, Strategy, Financing. 2009. World Health Organization. Available online at http://www.who.int/tb/publications/global_report/en/. Accessed on 30 April, 2009

[14] ibid

[15] ibid

[16] The WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance. 2008. Anti-tuberculosis drug resistance in the world. Fourth Global Report

[17] WHO Report 2009: Global Tuberculosis Control Epidemiology, Strategy, Financing. 2009. World Health Organization. Available online at http://www.who.int/tb/publications/global_report/en/. Accessed on 30 April, 2009

[18] ibid

[19] The WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance. 2008. Anti-tuberculosis drug resistance in the world. Fourth Global Report

[20] http://www.who.int/tb/challenges/xdr/xdr_map_sep09.pdf

[21] K. Senior. Relentless spread of extensively drug-resistant tuberculosis. The Lancet. Vol 9 July 2009

[22] The WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance. 2008. Anti-tuberculosis drug resistance in the world. Fourth Global Report

[23] Global tuberculosis control: epidemiology, strategy, financing : WHO report 2009. Available online at http://www.who.int/tb/publications/global_report/2009/pdf/full_report.pdf. Accessed May 14, 2009

[24] The WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance. 2008. Anti-tuberculosis drug resistance in the world. Fourth Global Report

[25] Bennett D., M. Myatt, S. Bertagnolio, D. Sutherland and C. Gilks. Recommendations for surveillance of transmitted HIV drug resistance in countries scaling-up antiretroviral treatment. Antiviral Therapy 13 Suppl. 2:25-36 2008; Ndembi N, F Lyagoba, B Nanteza, G Kushemererwa, J Serwanga, E Katongole-Mbidde, H Grosskurth and P Kaleebu. Transmitted antiretroviral drug resistance surveillance among newly HIV type 1-diagnosed women attending an antenatal clinic in Entebbe, Uganda. Aids Research and Human Retroviruses. Volume 24, Number 6, 2008

[26] http://www.medscape.com/viewarticle/498359

[27] UNICEF. http://www.unicef.org/health/index_malaria.html, accessed 14 April, 2009

[28] AM Dondorp, F Nosten, P Yi, D Das, A P Phyo, J Tarning, K M Lwin, F Ariey, W Hanpithakpong, S J. Lee, P Ringwald, K Silamut, M Imwong, K Chotivanich, P Lim, T Herdman, S S An, Shunmay Yeung, P Singhasivanon, N P.J. Day, N Lindegardh, D Socheat, and N J. White. Artemisinin Resistance in *Plasmodium falciparum* Malaria. New England Journal of Medicine, Volume 361:455-467

[29] Nugent R, J Pickett and E Back. Drug resistance as a global health policy priority. Drug Resistance Working Group Background Paper. Center for Global Development. Available online at http://www.cgdev.org/section/initiatives/_active/ghprn/workinggroups/drwg

[30] Jacobs, M. R., D. Felmingham, P. C. Appelbaum, R. N. Gr¸nebera, and the Alexander Project Group. 2003. ìThe Alexander Project 1998–2000: Susceptibility of Pathogens Isolated from Community-Acquired Respiratory Tract Infection to Commonly Used Antimicrobial Agents.î *Journal of Antimicrobial Chemotherapy* 52: 229–46.

[31] Kotloff KL, Winickoff JP, Ivanoff B, Clemens JD, Swerdlow DL, Sansonetti PJ, Adak GK, Levine MM. Global burden of Shigella infections: implications for vaccine development and implementation of control strategies. Bull World Health Organ. 77:651-666, 1999

[32] Okeke, I. et al. "Antimicrobial resistance in developing countries. Part I: recent trends and current status." Lancet Infectious Disease 2005:5

[33] Centers for Disease Control and Prevention. Mortality from Dysentery in Africa: A Follow-up Study in Burundi. Atlanta, Ga: Centers for Disease Control and Prevention; 1993. CDC internal report, Paquet C, Leborgne P, Sasse A, Varaine F. An outbreak of Shigella dysenterae type 1 dysentery in a refugee camp in Rwanda. Sante. 1995;5:181-184 and Paquet C, Van Soest M. Mortality and malnutrition
among Rwandan refugees in Zaıre. Lancet. 1994; 344:823-824 cited in Pecoul B, P Chirac, P Trouiller and J Pinel. Access to essential drugs in poor countries: a lost battle? JAMA 1999; 281: 361-367

[34] Sur, D., S. K. Niyogi, S. Sur, K. K. Datta, Y. Takeda, G. B. Nair, and S. K. Bhattacharya. 2003. Multidrug-resistant Shigella dysenteriae type 1: forerunners of a new epidemic strain in eastern India? Emerg Infect Dis 9:404-5 and Tjaniadi, P., M. Lesmana, D. Subekti, N. Machpud, S. Komalarini, W. Santoso, C. H. Simanjuntak, N. Punjabi, J. R. Campbell, W. K. Alexander, H. J. Beecham, 3rd, A. L. Corwin, and B. A. Oyofo. 2003. Antimicrobial resistance of bacterial pathogens associated with diarrheal patients in Indonesia. Am J Trop Med Hyg 68:666-70

[35] Estimated from PEPFAR and Global Fund expenditures at:
http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=28441 accessed December 4, 2008.

[36] Waring, B. et al, 2009, "Global Strategies to reduce the price of antiretroviral medicines: evidence from transactional databases," Bulletin of the World Health Organization 87, Geneva.

[37] WHO, Prioritizing second-line antiretroviral drugs for adults and adolescents: a public health approach. Report of a Working Group Meeting, Geneva, Switzerland, 21-22 May 2007.

[38] AIDS2031. 2009. The Cost of Antiretrovirals: Maximizing Value for Money, Results for Development Institute Working Paper 28, Washington, DC.

[39] Clinton Foundation, August 9, 2009.

[40] Waring, B. et al, 2009, "Global Strategies to reduce the price of antiretroviral medicines: evidence from transactional databases," Bulletin of the World Health Organization 87, Geneva.

[41] Waring, B. et al, 2009, "Global Strategies to reduce the price of antiretroviral medicines: evidence from transactional databases," Bulletin of the World Health Organization 87, Geneva.
[42] Keiser, O. et al, cited in AIDS 2031, 2009.
[43] Laing, R. and K. McGoldrick, 'Tuberculosis Drug Issues: Prices, Fixed Dose Combination Products and Second Line Drugs', Paper presented at the North American regional meeting of the International Union against Tuberculosis and Lung Disease, 2000.
[44]For lower estimate, see http://www.who.int/tb/features_archive/drs_factsheet.pdf For higher estimate, see Feasibility and Cost-Effectiveness of Treating Multidrug-Resistant Tuberculosis: A Cohort Study in the Philippines Tupasi TE, Gupta R, Quelapio MID, Orillaza RB, Mira NR, et al. PLoS Medicine Vol. 3, No. 9, e352 doi:10.1371/journal.pmed.0030352
[45] MMV, Understanding the Antimalarials Market: Uganda 2007, MMV Market Survey, August 2008.
[46] Talisuna, A, P. Grewal, JB Rwakimari, S Mukasa, G Jagoe, J Banerji. 2009. Cost is killing patients: subsidizing effective antimalarials. The Lancet, v. 374, No. 9697; 1224-1226
[47] Susan Foster, unpublished paper, Presented at the Global Forum on Health Research, Bamako Mali, November, 2008.
[48] Okeke, I. and R. Laxminaryan, 2005, Antimicrobial resistance in developing countries. Part I: recent trends and current status,"
[49] Smith R. et al, 2005, "Assessing the macroeconomic impact of healthcare problem: The application of computable general equilibrium analysis to antimicrobial resistance," Journal of Health Economics 24: 1055-1075.
[50] EMEA, 2009. The bacterial Challenge:Time to React. ECDC/EMEA Joint Technical Report, Accessed on September 23, 2009 at www.emea.europa.eu.
[51] Spellberg B, Miller LG, Kuo MN, Bradley J, Scheld WM, Edwards JE Jr. Societal costs versus savings from wild-card patent extension legislation to spur critically needed antibiotic development. Infection 2007;35(3):167-74
[52] http://www.stoptb.org/resource_center/assets/factsheets/factsheet_april08.pdf
[53] Medecines Sans Frontieres. 2006. Tuberculosis Diagnostics and Drug Sensitivity Testing. Paris.
[54] Goodman C., W. Brieger, A. Udwin, A. Mills, S. Meek and G. Greer. Medicine sellers and malaria treatment in sub-Saharan Africa: what do they do and how can their practice be improved? Am. J. Trop. Med. Hyg., 77(Suppl 6), 2007, pp.203-218
[55] Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet **2006**; 368:1575–80 and Andrews J. Clinical predictors of drug resistance and mortality among tuberculosis patients in a rural South African hospital: a case-control study. New Haven, CT: Yale AIDS Program, Department of Internal Medicine, Yale University School of Medicine, **2007**:79 cited in Andrews, JR, Shah NS, Gandhi N, Moll T and G Friedland. Multidrug-resistant and extensively drug-resistant tuberculosis: implications for the HIV epidemic and antiretroviral therapy rollout in South Africa. Journal of Infectious Diseases 2007:196 (Suppl 3).
[56] Berman P. Organization of ambulatory care provision: a critical determinant of health system performance in developing countries. *Bull WHO* 2000;78:791–802 cited in Brugha R. Antiretroviral treatment in developing countries: the peril of neglecting private providers. BMJ Volume 326. 21 June 2003.
[57] Kumarasamy N, S Safren, SR Raminani, R Pickard, R James, AK Sri Krishnan, S Solomon and K.H. Mayer. Barriers and facilitatros to Antiretroviral medication adherence among patients with HIV in Chennai, India: A Qualitative Study. AIDS APtients Care and STDs, Volume 19, Number 8, 2005
[58] Kumarasamy N, S Safren, SR Raminani, R Pickard, R James, AK Sri Krishnan, S Solomon and K.H. Mayer. Barriers and facilitatros to Antiretroviral medication adherence among patients with HIV in Chennai, India: A Qualitative Study. AIDS APtients Care and STDs, Volume 19, Number 8, 2005
[59] Kumarasamy N, S Safren, SR Raminani, R Pickard, R James, AK Sri Krishnan, S Solomon and K.H. Mayer. Barriers and facilitatros to Antiretroviral medication adherence among patients with HIV in Chennai, India: A Qualitative Study. AIDS APtients Care and STDs, Volume 19, Number 8, 2005

[60] Nordberg P, Stålsby Lundborg S and Göran Tomson. Consumers and providers—could they make better use of antibiotics? The Global Threat of Antibiotic Resistance: Exploring Roads towards Concerted Action. Background Document prepared for a Multidisciplinary meeting at the Dag Hammarskjöld Foundation. Uppsala, Sweden, 5-7 May 2004. Available online at http://mednet3.who.int/prioritymeds/report/append/Consumers_and_providers.pdf.

[61] Saple DG, Vaidya SB, Kharkar RD, Pandey VP, Vedrevu R, Ramnanai JP et al. Causes of ARV failure in India [abstract WePeB5860]. Proceedings of the 14th International AIDS conference, 7-12 July 2002, Barcelona

[62] Suniti Solomon, personal communication

[63] Reyburn H, Mbakilwa H, Mwangi R, Mwerinde O, Olomi R, Drakeley D, Whitty CJ, 2007. Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: a randomised trial. *BMJ 334:* 403.

[64] Harbarth S, Oberlander C. Do health care regulation and physician industry interaction influence antibiotic resisrates? The example of antimicrobial prescribing and dispensing in Japan. International Conference on Improving Use of Medicines. ChangMai, Thailand: World Health Organization; 2004.

[65] Macleod promotional flier

[66] Patient leaflet and drug box for Lupin's rifabutin product

[67] Berkelman R, Cassell G, Specter S, Hamburg M, Klugman K. The "Achilles Heel" of Global efforts to Combat Infectious Diseases. Clinical Infectious Diseases 2006; 42: 1503.

[68] Polage, C. R., G. Bedu-Addo, A. Owusu-Ofori, E. Frimpong, W. Lloyd, E. Zurcher, D. Hale, and C. A. Petti (2006) 'Laboratory Use in Ghana: Physician Perception and Practice' Am. J. Trop. Med. Hyg., 75(3), 2006, pp. 526–531

[69] Shin SS, Yagui M, Ascencios L, Yale G, Suarez C, Quispe N, et al. Scale-up of multidrug-resistant tuberculosis laboratory services, Peru. Emerg Infect Dis. 2008 May; 14(5): 701–708.

[70] WHO. 2009. Medicines use in primary care in developing and transitional countries. Geneva.

[71] FIP (2006) 'Global Pharmacy Workforce and Migration Report: a Call for Action'

[72] FIP (2009) 'Global Pharmacy Workforce Report'

[73] Bate et al, 2009, Pilot study comparing technologies to test for substandard drugs in field settings, African Journal of Pharmacy and Pharmacology

[74] UN Office on Drugs and Crime, July 2009, "Transnational Trafficking and the Rule of Law in West Africa: A Threat Assessment," Vienna.

[75] Pollan, M. "Our decrepit food factories," *New York Times Magazine.* December 16, 2007.

[76] Ogunleye, A. O., M. A. Oyekunle, A. O. Sonibare "Multidrug resistant *Escherichia coli* isolates of poultry origin in Abeokuta, South Western Nigeria." Vet. arhiv 78, 501-509, 2008.

[77] Okoli Ifeanyi, C., E. G. Ndujihe and P. I. Ogbuewu *Frequency Of Isolation Of Salmonella From Commercial Poultry Feeds And Their Anti-Microbial Resistance Profiles, Imo State, Nigeria.* 2006

[78] M. A. Dipeolu and D. O. Alonge "Residues of streptomycin antibiotic in meat sold for human consumption in some states of SW Nigeria" *Archivos de Zootencia*, diciembre año/vol. 51, número 196, Universidad de Córdoba España. 2002

[79] Union of Concerned Scientists. "European Union Bans Antibiotics for Growth Promotion." http://www.ucsusa.org/food_and_environment/antibiotics_and_food/european-union-ban.html

[80] Nelson, J M, Chiller, T M, Powers, J H and Frederick J Angulo "Fluoroquinolone-resistant *Campylobacter* species and the withdrawal of Fluoroquinolones from Use in Poultry: A Public Health Success Story," *Clinical Infectious Diseases* 2007:44 (1 April) 977-80

[81] WHO 'Tackling antimicrobial resistance: the third global patient safety challenge' http://www.who.int/patientsafety/amr/en/

[82] Jane Parry, WHO Bulletin 2009; 87: 493-494.

[83] AFP 'Economic crisis hurts HIV fight: World Bank, UN' 6 July 2009 http://www.google.com/hostednews/afp/article/ALeqM5jqJqtbEdRrBwh1CiV2LOsC-h4FwA

[84] 'Koeth, L M and Miller L A Evolving Concepts of Pharmaceutical Company–Sponsored Surveillance Studies Clinical Infectious Diseases 2005 41:s4, S279-S282

[85] http://www.ansorp.org/

[86] http://www.who.int/drugresistance/whonetsoftware/en/
[87] CDC 'Laboratory Accreditation Program a Historic Step to Strengthen Health Systems' http://www.cdc.gov/globalAIDS/laboratory/lab-accreditation.html
[88] Hutton, D "Cooperating for a worthy cause" Drug Discovery News November 2008 http://www.drugdiscoverynews.com/index.php?newsarticle=2554
[89] 2004 2nd International Conference on Improving Use of Medicines (ICIUM) recommendations on consumer drug use practices.; See also http://www.icium.org/icium2004/recommendations.asp - see "Community-based interventions" file.
[90] Center for Pharmaceutical Management. 2008. Accredited Drug Dispensing Outlets in Tanzania Strategies for Enhancing Access to Medicines Program. Prepared for the Strategies for Enhancing Access to Medicines Program. Arlington, VA: Management Sciences for Health; Health Research for Action. "Review of the Accredited Drug Dispensing Outlets Roll-Out Program in Tanzania." (2006); E. Alphonse. Accredited drug dispensing outlets (ADDO) program in Tanzania. Presentation.
[91] Center for Pharmaceutical Management. 2008. Accredited Drug Dispensing Outlets in Tanzania Strategies for Enhancing Access to Medicines Program. Prepared for the Strategies for Enhancing Access to Medicines Program. Arlington, VA: Management Sciences for Health.)
[92] Marsh VM, Mutemi WM, Willets A, Bayah K, Were S, Ross A, Marsh K, 2004. Improving malaria home treatment by training drug retailers in rural Kenya. *Trop Med Int Health 9:* 451–460 and Goodman C., W. Brieger, A. Udwin, A. Mills, S. Meek and G. Greer. Medicine sellers and malaria treatment in sub-Saharan Africa: what do they do and how can their practice be improved? *Am. J. Trop. Med. Hyg*., 77(Suppl 6), 2007, pp.203-218
[93] ibid.
[94] Tavrow P, Shabahang J, Makama S, 2003. Vendor to vendor education to improve malaria treatment by private drug outlets in Bungoma District, Kenya. Malar J 2: 1-10 and Goodman C., W. Brieger, A. Udwin, A. Mills, S. Meek and G. Greer. Medicine sellers and malaria treatment in sub-Saharan Africa: what do they do and how can their practice be improved? *Am. J. Trop. Med. Hyg*., 77(Suppl 6), 2007, pp.203-218
[95] http://www.icium.org/icium2004/recommendations.asp. See "Policies and Programmes to Improve Use of Medicines: Recommendations from ICIUM 2004" file.
[96] ibid.
[97] World Bank, The Development Potential of Regional Programs, Independent Evaluation Group, 2007, Washington. http://siteresources.worldbank.org/EXTREGPROPART/Resources/reg_pgms_full.pdf. Accessed on December 5, 2008.
[98] Davis, D., M.A. O'Brien, N. Freemantle, et al. 1999. Impact of formal continuing medical education: do conferences, workshops, rounds, and other traditional continuing education activities change physician behavior or health outcomes? JAMA 282:867-874
[99] ibid.
[100] Walker, B et al., Looming Global-Scale Failures and Missing Institutions, Science, v. 325; 11 September 2009, p. 1345-46.