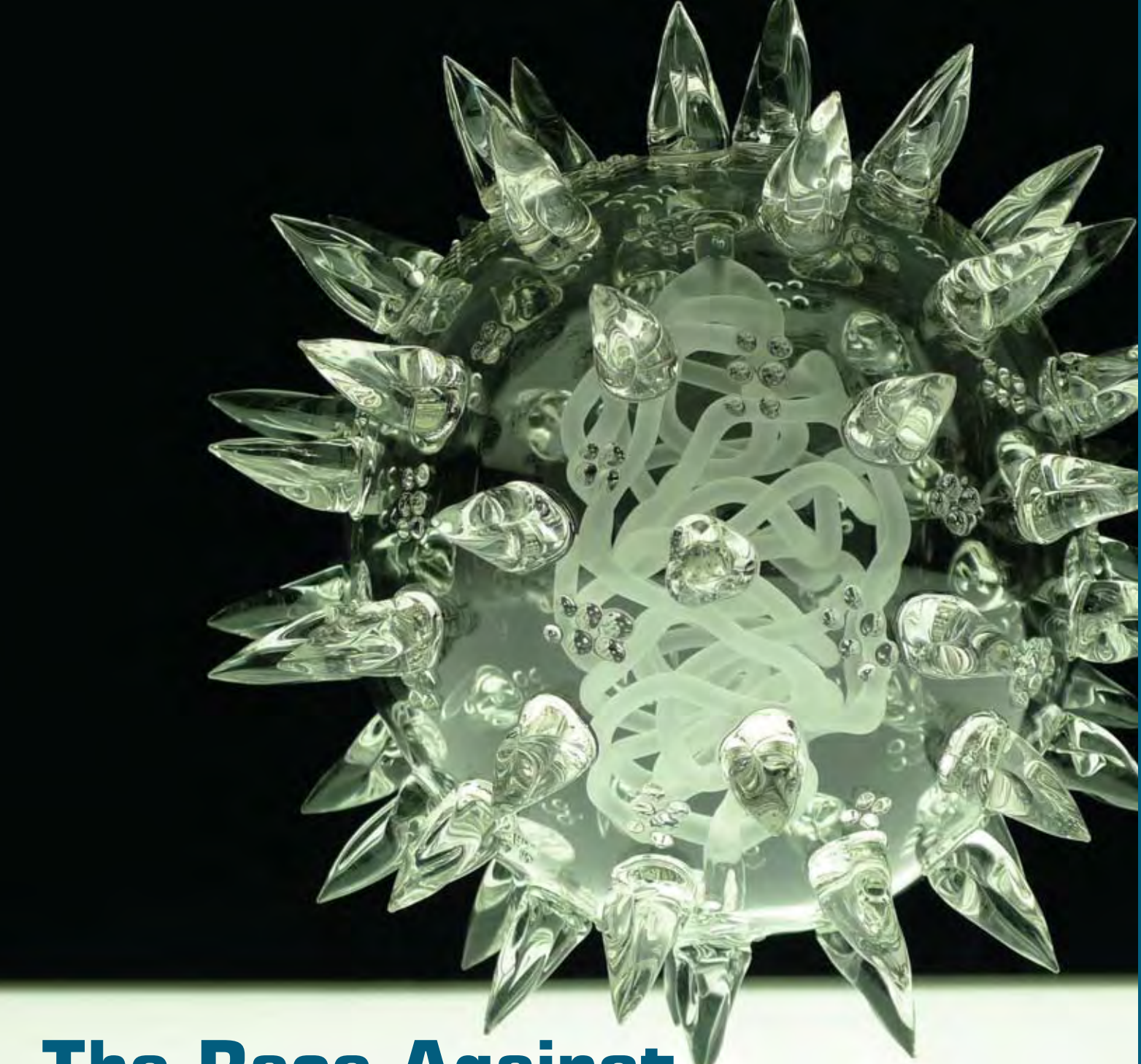

The Race Against Drug Resistance

A Report of the Center for Global Development's Drug Resistance Working Group

Rachel Nugent
Emma Back
Alexandra Beith

When Medicines Fail
A GLOBAL PUSH TO FIGHT DRUG RESISTANCE

Center for Global Development

Contents at a glance

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Praise for **The Race Against Drug Resistance**

"The dwindling effectiveness of medicines against infectious diseases caused by the development of drug resistance is one of the most important public health issues of the early 21st century. This report clearly highlights the issues based on a presentation of solid science, wise policy analysis, and compelling advocacy. It lays the groundwork necessary for a major thrust from global, national, and local health authorities to give resistance the attention it deserves. People who care about the future of people's health should read this timely and forward-looking report."

Dr. David Heymann
Former Assistant Director-General for Health Security and Environment, World Health Organization; currently, Director, Centre on Global Health Security, Chatham House

"This must-read report lays out the global threat of resistant microbes across all infectious diseases—what we call a "Shadow Epidemic." It illustrates the interactive factors driving the problem and opportunities for donors, funders, and infectious disease networks to work together to control and reverse resistance."

Dr. Stuart B. Levy
President, Alliance for the Prudent Use of Antibiotics; Professor of Molecular Biology / Microbiology and Medicine, Tufts University School of Medicine

"Antibiotics are a global resource and the world has a responsibility to use this resource for the greatest good of humanity while protecting their effectiveness. CGD's new report puts this issue front and center and offers a valuable set of recommendations to extend the power of drugs to fight infectious diseases."

Dr. Ramanan Laxminarayan
Senior Fellow and Director of the Center for Disease Dynamics, Economics, and Policy, Resources for the Future

"Drug resistance is a major public health problem that requires multiple solutions. We urgently need improved incentives to develop new drugs. However, new drugs alone will not be the answer to the problem. We must also use more carefully the drugs we already have, eliminate sub-standard drugs from supply chains, and strengthen the public health and clinical responses to drug resistance. This report offers concrete actions to accomplish those goals. It is a welcome contribution to the global fight against drug resistance."

Dr. Otto Cars
Chairman, ReAct—Action on Antibiotic Resistance

"FIP welcomes this powerful report. Given the critical role that drug prescribers and dispensers play in influencing medicine use—and hence drug resistance—FIP strongly supports the creation of a global partnership to promote appropriate medicines use, which will be of great value to society as a whole. FIP stands ready to participate and calls upon governments and key international stakeholders to support the recommendations in this report as part of a multi-faceted strategy that can significantly reduce the global spread of drug resistance."

Ton Hoek
CEO, International Pharmaceutical Federation (FIP)

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Members of the Working Group were invited to join in a personal capacity and on a voluntary basis. The report of the Working Group reflects a consensus among the members listed above. This report does not necessarily represent the views of the organizations with which the Working Group members are affiliated, the Center for Global Development's funders or the Board of Directors.

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Terms and acronyms

Acquired (*de novo*) resistance—a resistant strain appearing spontaneously in a single patient

ACTs—artemisinin-based combination therapies

ADDOs—accredited drug dispensing outlets

AMFm—Affordable Medicines Facility—malaria

AMR—antimicrobial resistance

APUA—Alliance for the Prudent Use of Antibiotics

ART—antiretroviral therapy

ARVs—antiretrovirals (drugs)

CDC—U.S. Centers for Disease Control and Prevention

CGD—Center for Global Development

Counterfeit drug—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 subtherapeutic amount of active pharmaceutical ingredient (and thus also be substandard), no active ingredient, or an inappropriate active ingredient.

DFID—UK Department for International Development

DSTs—drug susceptibility tests

IHRs—International Health Regulations

ISO—International Organization for Standardization

MDR-TB—multi-drug-resistant tuberculosis

MRSA—methicillin-resistant *Staphylococcus aureus*

NEPAD—New Partnership for Africa's Development

NDRAs—national drug regulatory agencies

NGO—nongovernmental organization

NIH—U.S. National Institutes of Health

PAHO—Pan-American Health Organization

PDPs—product development partnerships

Primary resistance—Transmission of resistant strains from an infectious case to other persons, which causes a case of the disease that is drug resistant from the outset.

R&D—research and development

SARS—severe acute respiratory syndrome

SP—sulfadoxine-pyrimethamine

TB—tuberculosis

UNAIDS—Joint United Nations Program on HIV/AIDS

UNFPA—United Nations Population Fund

UNICEF—United Nations Children's Fund

UNITAID—International Drug Purchase Facility

USAID—U.S. Agency for International Development

WADRAN—West African Drug Regulatory Authority Network

WHO—World Health Organization

XDR-TB—extensively drug-resistant tuberculosis

Preface

In an increasingly interconnected world, problems with drug resistance have moved from the patient's bedside to threaten global public health. Drug resistance has dramatically increased the costs of fighting tuberculosis (TB) and malaria, has slowed gains against childhood dysentery and pneumonia, and threatens to undermine the push to treat people living with HIV/AIDS effectively. Global health funders and development agencies have cause to worry about whether their investments in access to drugs, and global health programming more broadly, are being undone by the relentless advance of drug resistance.

Drug resistance is an extremely serious problem that is today undermining effective health care for millions of people and threatens to grow worse—yet it doesn't receive serious attention. On a technical level, this is because drug efficacy is a common property resource—one that is difficult to bar people from using, but that does run out if we overuse it. We all want to believe that the drugs we rely upon will keep working no matter how much we use them—or misuse them. Further, many actors make decisions that determine the trajectory of drug resistance that impose invisible costs to society, thereby lulling us into complacency. On a human level, it is hard to see that people are dying from drug resistance—but they are. As with climate change, we now understand the science of drug resistance well enough to act, but the policy response has eluded us.

The Center for Global Development's global health work focuses on issues where donors can benefit from expert technical advice and detailed analysis to guide decisions about resource investments. This report is an example. The Drug Resistance Working Group[i] was convened in late 2007 to identify practical and feasible ways for donors, multilateral organizations, nongovernmental organizations, and private companies to prevent or contain resistance to drugs for infectious diseases affecting developing countries.

The highly accomplished members of the Working Group came to this task with a wide range of specialized knowledge. They acknowledged the difficulties of tackling drug resistance from a perch in Washington, Boston, London, and even Accra, but insisted that the recommendations include both global actions and local solutions that hold the potential to alter the culture of how we use medicines worldwide. In the course of their discussions, Working Group members carefully examined the common drivers of drug resistance that plague treatment efforts for many infectious diseases, particularly in developing countries. As a result, their recommendations emphasize common, cross-disease approaches, rather than vertical, disease-specific actions.

The Working Group drew from earlier laudable reports and a wide range of other sources to develop a set of interlocking recommendations that bring together familiar ideas with new twists and new ideas that are likely to challenge many assumptions. They include steps that individually could go far to improve treatment of life-threatening diseases around the world. Collectively, these steps define both the foundation and the actions necessary to assure that the cures we seek are cures that will work.

This report will explain in detail the major drivers of drug resistance, the many laudable but completely insufficient efforts from health officials and funders at all levels to take control of the problem, and the enormous costs to society, both financial and in lost lives, of our current approaches. The report offers four recommendations, chosen from among many possible responses, as those with the most promise to slow the advance of drug resistance. Now it is time for all concerned about global health to make drug resistance a priority.

Nancy Birdsall
President
Center for Global Development

i. See appendixes C and D and www.WhenMedicinesFail.org to learn more about the members of the Drug Resistance Working Group and their objectives and process.

Acknowledgments

This report was possible only through the hard work and dedication of a host of individuals. First and foremost, we thank the members of the Drug Resistance Working Group, who spent more than two years considering how the international community can better ensure that life-saving drugs can do just that for years to come. The diverse experiences and expertise of Working Group members allowed us to challenge and learn from one another, and most important, to agree on how to sustain drug efficacy. Working Group members are profiled in appendix D.

The ideas for this report were shaped by informative background papers prepared by Emma Back, Alexandra Beith, Jorn Sonderholm, Jessica Pickett, and Prashant Yadav. We extend sincere thanks to them for providing the Working Group with helpful analysis and advice that guided our work from the early stages.

We are grateful to the many people who offered feedback and edits on this and earlier drafts of the report. We are particularly appreciative of Andrew Ramsay for organizing a briefing at the World Health Organization; to Carol Medlin and members of the global health staff at the Bill & Melinda Gates Foundation for their input; and to participants in consultation meetings held during the 2008 Global Forum on Health Research (Bamako, Mali) and during the 2008 IUATLD meeting in Paris, France. In addition, we would like to thank the many audiences with whom this work was shared and debated during conferences, workshops, and other presentation venues.

Private interviews and individual correspondence also informed this report. Over two years, hundreds of people offered their advice and expertise and helped us think through the many intricacies of the problem of drug resistance. We are indebted to each and every one of them. A partial list of people and organizations consulted is in appendix E. We regret any omissions.

Closer to home, wonderful colleagues at the Center for Global Development provided valuable feedback throughout our research, consultation, and writing stages. This report has benefited greatly from their ideas and insights. In particular, we'd like to thank Jessica Pickett, Scott Kniaz, Katie Stein, Laura Drachsler, Steve Perlow, John Osterman, Lawrence McDonald, Ruth Levine, Mead Over, and April Harding.

Last, we thank the Bill & Melinda Gates Foundation for its financial support and engagement throughout this project. Specifically, Thomas Kanyok, Carol Medlin, and Renee Ridzon provided essential insights into the direction of the report in the context of major global health efforts at the Foundation and more broadly.

Any errors or omissions of fact remain the responsibility of the authors.

Executive summary

Over the past decade, governments and private funders have worked tirelessly to increase access to drugs in developing countries, particularly for malaria, HIV, and tuberculosis (TB). Indeed, in recent years the purchase of drugs accounts for up to 40 percent of development assistance from the Global Fund to Fight AIDS, Tuberculosis and Malaria and other major health donors. These welcome efforts have saved many lives—but are short-sighted. The global health community must turn its attention to ensuring both broad access to drugs and lasting effectiveness of treatment.

We are losing our ability to cure common diseases to an invisible adversary: the drug resistant bug. Drug resistance occurs when microbes adapt to survive in the presence of drug therapy. Although this is a natural, evolutionary phenomenon, humans have hastened resistance.

Across the world, drug resistance is on the rise. A vigorous effort to tackle this problem, the severity of which is little recognized, must start with an immediate injection of leadership from governments, donors, global health institutions, and industry.

Consequences of drug resistance

Drug resistance costs lives, and the consequences can be most profound for children, who are especially susceptible to infectious diseases. The most common childhood diseases in developing countries—malaria, pneumonia, other respiratory infections, and dysentery—are no longer curable by many of the older antibiotics or other drugs available in poor countries. The consequences are devastating: bacterial acute respiratory infections, for example, kill more than three million children every year and malaria kills two million children. Many cases of these illnesses are caused by strains now resistant to common drugs. In wealthier countries, hospitals are reeling from an explosion of methicillin-resistant *Staphylococcus aureas* (MRSA). From 1974 to 2004, MRSA prevalence increased from roughly 2 percent to more than 50 percent of staph infections in many U.S. hospitals, resulting in tens of thousands of deaths.

Resistance to drugs also has a startling impact on the cost of curing patients. In many poor countries, expenditures for drugs represent a large proportion of overall health-care costs, ranging from 20 to 60 percent of total expenditure on health. When first-line drugs fail, second-line alternative drugs are almost always far more costly and require greater medical oversight. For example, it costs as much to cure one patient of extensively drug-resistant TB as it does to cure 200 patients of susceptible TB. Where resources are finite or severely inadequate, for every person put on second-line treatment, far fewer people can be given life-saving or life-extending care.

The costs of global inaction are borne in the short term by those stricken with a resistant form of disease who lack either access to health services or the money to pay for more costly, second-line treatments. In the longer term, the consequences are shouldered by all of us—and by future generations—who must rely on a shrinking collection of medicines that work.

Commonalities among resistance drivers

There are many drivers—both naturally occurring and human-made—that determine resistance transmission and emergence. Pathogens find numerous ways to survive an attack from drugs designed to kill them; specific disease characteristics also affect the processes through which resistance arises. Drug characteristics, therapeutic protocols, and drug selling and purchasing practices all mediate the relationship between bugs and drugs, and between patient and health-care provider, determining whether resistance will occur. These characteristics vary by disease and environment, but there are also important commonalities in the major drivers of resistance across diseases and drugs, patients and providers. In those commonalities lies the greatest opportunity to identify policy solutions. This report, for the first time, identifies common drivers of resistance across diseases and offers common solutions.

Four critical steps for fighting drug resistance

Over the past decade, the global community has responded to the rise in drug-resistant organisms with a number of disease- or country-specific initiatives. Some have been more successful than others, but none have addressed the problem on a global scale across diseases. The growing threat of drug resistance demands an extensive and systematic global response. A beginning was signaled in late 2007 when the Center for Global Development convened an expert Drug Resistance Working Group to identify practical ways for pharmaceutical companies, governments, donors, and global health institutions to collectively combat global drug resistance, particularly in high-burden diseases affecting developing countries.

The recommendations of the Working Group focus on problems created by market and institutional failures and where evidence for successful action is strong. Taking account of current

data and resource limitations, the Working Group coalesced on actions that, taken together, will go far to contain and reduce drug resistance globally. They target four critical areas: surveillance and laboratory capacity; drug supply chain integrity; regulatory capacity; and the technology pipeline. Each has merit individually—but their strength lies in taking a unified, multifaceted approach, with both public- and private-sector involvement.

In addition to the four high-priority recommendations described below, the Working Group calls for research and action on several other important aspects of drug resistance not addressed here. In some cases, other reputable organizations are tackling those issues, and in others, the data and evidence needed to understand them are missing. These include the need to quantify the full economic impacts of resistance, understand the effects of using therapeutic drugs to prevent transmission, comprehend the scale and impact of extensive antibiotic use in animals and agriculture, and banish drug counterfeiting.

Recommendation #1
Improve surveillance by collecting and sharing resistance information across networks of laboratories

Efforts to tackle drug resistance are complicated by enormous gaps in our knowledge of where resistance lurks and how it spreads. Take the example of TB: It is estimated that fewer than one in 10 cases of resistant TB are currently detected and even fewer are treated. The lack of systematic data leads to a circle of neglect: Insufficient awareness makes drug resistance a low priority for donors and governments, while a lack of attention and resources keep hidden the evidence required to address drug resistance in a focused manner.

The shared resource of drug efficacy cannot be protected without collective action, and a first step is to develop a shared view of the problem—a common understanding of when, where, how, and why drug resistance is emerging and spreading. 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.

The Working Group recommends that global health donors and technical agencies work with developing country governments to establish a multi-disease surveillance network that can track the emergence and spread of drug-resistant strains of diseases and develop accessible and meaningful data-sharing platforms for multiple audiences, including policymakers and global health donors. A growing number of developing countries have improved laboratory capacities and surveillance; however, these efforts are disease-specific and most target either TB or HIV/AIDS. Given the common drivers of drug resistance across

Recommendations
Old problems and new solutions to global drug resistance

Because . . .	We propose . . .
Drug resistance testing and surveillance capabilities are inadequate	Low-cost formal and innovative informal surveillance to fill the information gap and broaden disease testing with new laboratory technology
Weak points in the supply chain and inappropriate dispensing facilitate drug resistance	Better incentives for accountability from drug and diagnostics manufacturers, prescribers, and dispensers to reduce drug resistance
Drug regulation is weak and uncertain	Strengthening regulators through support to regional networks
There are many ideas to create incentives for R&D for neglected diseases	Stimulating research for resistance-specific technology development

diseases, the Working Group recommends that those groups and networks working on existing disease-specific efforts and focused on surveillance collaborate to make best use of scarce capacity and identify resistance across diseases.

But simply gathering good information is not enough. The system must ultimately enhance public health knowledge and guide policy making at national and regional levels, while informing patient diagnosis and care at the local level. Three concrete outcomes can quickly build on an improved drug resistance knowledge base: (i) a biennial Global Drug Resistance report; (ii) a Web-based resource center to aggregate and share data; and (iii) the World Health Organization can provide direction to countries on when and how to report on the emergence or transmission of drug-resistant forms of diseases.

Recommendation #2
Secure the drug supply chain to ensure quality products and practices

The supply chain extends from manufacturers to patients, each step along the way presenting the potential for breaches that contribute to drug resistance. Drug resistance will be slowed only by tightening the *entire* supply chain with the cooperation of the public and private sectors, both upstream and down. The Working Group recommends a two-pronged approach: upstream post-marketing quality standards for manufacturers and downstream rational use and certification standards for those who prescribe and dispense drugs.

Upstream: Companies producing and distributing medicines and diagnostics need a uniform set of standards to assure that product quality is tested and maintained *after* it leaves the factory. The International Organization of Standardization (ISO) should work with companies and technical agencies to create voluntary standards. They would encourage rigorous and transparent procedures for testing and reporting on the quality of drugs and diagnostics—ultimately reducing the circulation of poor-quality products and restoring confidence in the quality of the global supply chain. The standards may include other practices and agreed-upon outcomes for responsible companies to ensure that only high-quality products reach the retail market. Achieving ISO certification of these steps would grant those companies a market advantage over competitors that do not meet standards and exert pressure on the entire industry to elevate its efforts to preserve the quality of drugs and diagnostics. ISO certification should become a procurement requirement of all donor organizations and national governments making drug purchases with donor funds.

Downstream: From roadside drug sellers to licensed doctors, the expertise of drug providers varies greatly—yet all need the knowledge and tools to ensure that drugs are prescribed, dispensed, and taken properly. A *Global Partnership of Medicine Providers* is needed to collect and promote best practices in drug prescribing and dispensing and share rigorous evaluation of what works. The partnership would:

- create a global knowledge repository of proven tools to improve prescribing and dispensing practices;
- develop pharmaceutical and health provider educational curricula on best practices;
- offer a global technical assistance platform for countries to improve and evaluate prescribing and dispensing practices; and
- identify financial resources to replicate successful programs, pilot new programs, and implement country-specific interventions.

Partnership is also needed at the local level. *National Partnerships of Medicine Providers* should be developed to adapt the tested models to individual countries and link country efforts to financial resources.

Securing the supply chain—both at the local and global levels, and both upstream and downstream—is a substantial undertaking and will take focused collaboration among many different stakeholders. But, without it, drug resistance will continue to grow and millions of lives will remain at risk, now and well into the future.

Recommendation #3
Strengthen national drug regulatory authorities in developing countries

In developing countries, national drug regulatory authorities (NDRAs) face the daunting task of monitoring the flow of drugs within and across their borders, often constrained by severely limited resources. Without adequate staffing and funding, many NDRAs lack the ability to track the circulation of drugs within and across borders and have little capacity to enforce drug quality standards. And without proper enforcement, poor-quality and counterfeit drugs can easily reach unknowing patients, acting as catalysts of drug resistance.

The Working Group recommends that national and international support be provided to create new regional networks of national drug regulators, enhance existing ones, and exploit shared incentives to protect drug efficacy. This support should be channeled through the ongoing regulatory harmonization and strengthening initiatives of global health donors, including the Global Fund to Fight AIDS, Tuberculosis and Malaria, the Hanshep Initiative of the UK Department for International Development (DFID), and others. By collaborating, NDRAs operating in the same region will enhance their ability to track sub-standard and counterfeit drugs, coordinate inspections and border control of drug flows, build internal capacity to accomplish more with existing resources, and align drug policies and treatment guidelines. A regional approach is all the more important as country boundaries become increasingly porous. The regional networks will be an impetus for joint decision making among regulatory agencies charged with maintaining a safe and high-quality drug supply.

Recommendation #4
Catalyze research and innovation to speed the development of resistance-fighting technologies

Infectious disease research and development—particularly for drugs and vaccines—was highly productive during the 20th century. But in the past decade, approvals of new drugs declined and many large pharmaceutical companies reduced or sold their anti-infective portfolios. Further, other tools that improve treatment—particularly rapid diagnostics—received little attention until recently. For some diseases, pipelines have remained so thin that old treatments are all we have. For example, there has been no new first-line TB drug for 50 years, and this has given the microbe ample time to evolve resistant strains. Penicillin, once considered a wonder drug, now effectively treats only one-half to two-thirds of *S. pneumoniae* strains in many developed and developing countries, and less than one-quarter in certain regions. The development of improved diagnostics and susceptibility tests as well as preventive and resistance-fighting technologies could help prescribers choose the appropriate medicines and help slow resistance.

New attention is being paid to the implications of resistance on drug pipelines, but more is needed. There is ample evidence to suggest there is a significant pent-up supply of resistant-relevant research, but researchers working in this area are in need of funding and support to advance their ideas, discoveries, and innovations.

The Working Group recommends the creation of a Web-based marketplace to showcase resistance-relevant research and innovation across diseases. It would offer a brokerage facility to provide technical assistance, connect researchers with one another, and match good ideas with investors. The facility would lower the transaction costs of research collaboration and partnership by offering a way for researchers to virtually share their knowledge and collaborate on resistance-specific technologies. For pharmaceutical companies, venture capitalists, foundations, and public funders seeking to take viable technologies to consumers, the marketplace could incubate new ideas.

The urgent need for global action

We have the means to slow the advance of drug resistance, and the steps recommended by the Working Group will help strengthen our tenuous grasp on drug efficacy. Now, coordinated, collective action is needed to bring the recommendations to fruition.

Donors and philanthropic organizations need to ensure that their laudable efforts to increase access to drugs in the developing world are accompanied by measures to protect the continued efficacy of drug treatment. They must strenuously enforce quality standards throughout the supply chain, ensure that adequate knowledge is gathered about the effectiveness of the medicines they are providing, and strengthen the key components of health systems that can better deter resistance emergence and spread.

Companies need to prioritize resistance reduction in their research and development strategies, and ensure that their products remain of the highest quality throughout the distribution process. A set of voluntary industry standards to ensure post-marketing quality would reduce the circulation of poor-quality drugs and diagnostics and discover weaknesses in supplies before they reach patients.

Governments have a responsibility to provide regulation and oversight of distribution and use, as well as to properly support public health laboratory facilities and surveillance systems to detect and monitor drug efficacy. Improved or new regional regulatory networks will allow national governments to align

their policies and knowledge and accomplish more with existing resources. Developed country governments should aggressively fight drug resistance both to protect the health of their own citizens and to ensure global health goals are met. Resistance should be core to health system strengthening. Two immediate steps are to expand the new U.S.-E.U. Task Force on Antimicrobial Resistance into a global task force, and to promote Antibiotic Resistance Day throughout the world.

Global health institutions must make drug resistance a priority —across all treatable diseases—by providing financial and technical support to developing nations to meet and maintain standards. WHO must clearly articulate countries' responsibilities regarding resistance under the global health legal framework.

Patients, prescribers, and *dispensers* must all gain greater awareness of the personal and social costs of drug resistance, and employ far greater diligence in appropriately using drugs.

We can no longer afford to be indifferent to the spread of drug-resistant diseases. We must show collective leadership if we are to meet this challenge. For the sake of all people who seek effective health care, now and in the future, drug resistance must be addressed urgently and aggressively as a global health priority.

1
Drug resistance: a global-scale failure

Chapter at a glance

- Drug resistance is on the rise globally, imposing immediate health and economic consequences on patients and health care systems.
- As access to essential medicines continues to expand in the developing world, it must be accompanied by specific measures to ensure the safety, efficacy, sustainability, and appropriate use of those drugs.
- Tackling resistance effectively is challenged by huge gaps in our knowledge as to where resistance lurks and how it is spreading.
- Drug resistance continues to be tackled one disease at a time through small-scale and uncoordinated efforts, even though the major drivers of resistance are similar across diseases.
- Slowing drug resistance is possible, but will require coordinated commitments and actions from public and private institutions.

The long-term consequences of drug resistance—recently called a "global-scale failure"[1]—are hard to identify. What we do know is that the immediate health and economic consequences are terribly high. The costs of global inaction in targeting resistance are borne in the near term by those who are stricken with resistant infections and lack access to health services or the financial capacity to obtain the 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 diseases. The broad sweep of drug resistance makes increasingly urgent the successful development of new products—a costly, slow, and uncertain process. But new drugs alone will not be sufficient.

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 and supplies accounts for up to 40 percent of development assistance from some major health donors[2]—they do far less to protect and preserve the efficacy of those drugs.[3] Regrettably, the practices of those who are seeking to expand access can unintentionally accelerate the spread of resistance by making drugs widely available where conditions for assuring quality and appropriate use are weak. 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.

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.[i] Indeed, many diseases common in developing countries —including malaria, pneumonia, cholera, and dysentery—are increasingly caused by strains that are resistant to multiple drugs. This is true for diseases such as tuberculosis (TB) and infections such as *Staphylococcus aureus (S. aureus)* that afflict rich countries as well as poor ones.

The problem is global: Drug-resistant TB is spreading rapidly to countries where it has not been seen before.[4] All currently available antimalarials, including artemisinin-based combination therapies (ACTs), have shown declining efficacy that could precipitate a global health crisis if it becomes widespread.[5] The solutions must be global as well, and must transcend specific bacteria. Achieving better health through drug treatment cannot be done one disease at a time.

The sheer availability and use of drugs are strongly linked to the emergence and spread of pathogens resistant to those drugs. Examples abound from developed countries where data on resistance are more complete. Levels of fluoroquinolone use have been strongly associated with ciprofloxacin resistance for *Klebsiella pneumoniae, E. coli,* and *Proteus mirabilis* measured at the population level in British Columbia.[6] A U.S. study found that increased macrolide use from 1995 to 1999 corresponded with a doubling of the proportion of macrolide-resistant pneumococci.[7] Figure 1.1 illustrates a close relationship between penicillin-resistant *Streptococcus pneumoniae (S. pneumoniae)* and total antibiotic use for a number of countries in Europe, the United States, and Canada.

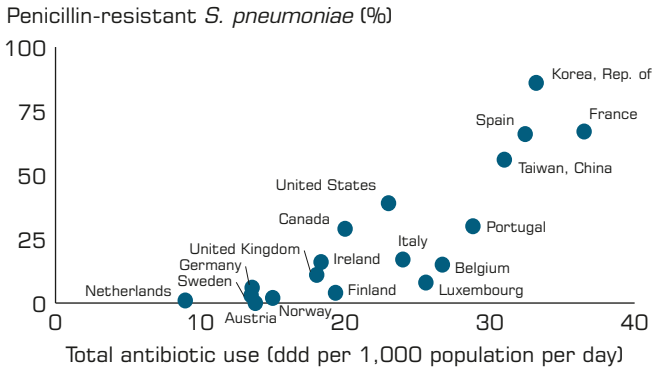
Drug resistance, though not a new problem, has been hastened by rapid increases in drug access and, all too often, inappropriate or suboptimal use of drugs around the world. In many ways, it is one of the costs of the tremendous success of expanding access to needed medicines. The number of people being treated for HIV/AIDS, for example, increased 10-fold between 2002 and 2007;[ii,8] there was an 8-fold rise in deliveries of ACTs for malaria treatment between 2005 and 2006,[9] 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.[10] 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, sustainability, and appropriate use of those drugs for a larger group of patients.**

i. While recognizing that resistance inhibits treatment of many illnesses, because of space constraints this report emphasizes resistance in the treatment of a handful of specific diseases: TB, malaria, HIV/AIDS, pneumonia, and shigellosis.

ii. Nearly 4 million people living with HIV/AIDS are currently receiving treatment in low- and middle-income countries. This figure represents a large increase in recent years, from 2 percent of those who required antiretroviral therapy receiving it in 2003 to 45 percent of those estimated to be in need in 2008.

The most lethal childhood diseases frequently no longer respond to standard treatment

Figure 1.1
Relationship between penicillin-resistant *S. pneumoniae* and total antibiotic use by country



Note: ddd is defined daily dose.

Source: Albrich, Mannet, and Harbarth (2004).

Knowledge gaps are large

Tackling resistance effectively is complicated by enormous gaps in our knowledge about where resistance lurks and how it is spreading. 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. Figure 1.2 is a composite snapshot of drug resistance data relating to selected infectious diseases across the world. The limited information that is available to map based on estimates and small-scale studies reveals how extremely (and dangerously) weak our current knowledge about drug resistance prevalence is.

Take the example of TB: It is estimated that fewer than 1 in 10 cases of resistant TB is currently detected, and less than 2 percent of known multi-drug-resistant TB (MDR-TB[iii]) cases in high-burden countries are treated according to the World Health Organization (WHO) guidelines.[11] Experts have pointed out that these figures merely "scratch the surface of our ignorance."[12] This means that hundreds of thousands of people are infected with drug-resistant TB but do not know it. Many known resistant infections go untreated, or are treated with ineffective drugs, thereby spurring the development of more resistant forms.

Health consequences

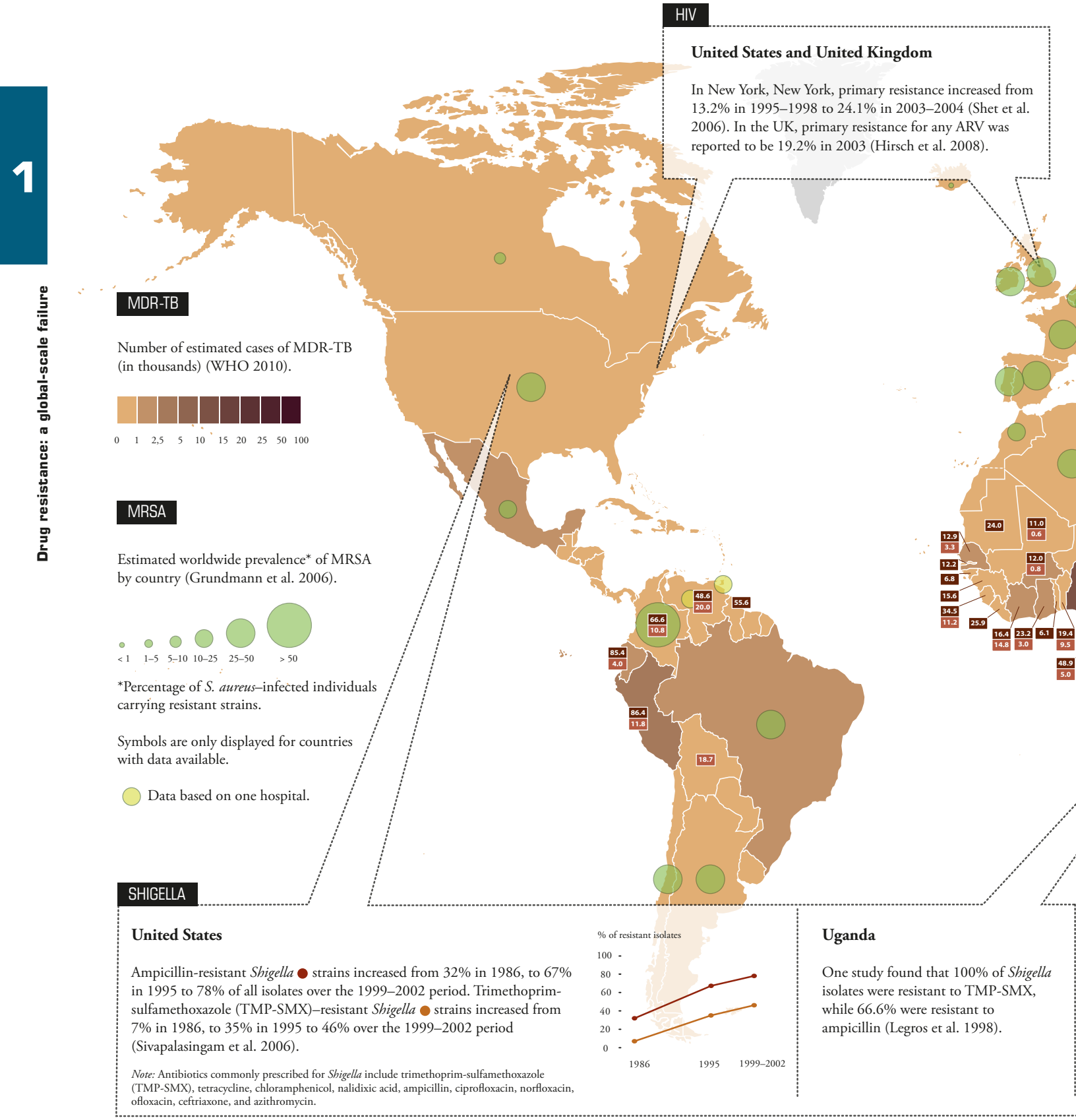
Children are particularly vulnerable to infectious diseases. When drug resistance slows or prevents effective treatment, they are more likely to suffer long-term damage or die. The most lethal childhood diseases—malaria, pneumonia and other respiratory infections, and dysentery—frequently no longer respond to standard treatment, and more effective drugs are often not available in poor countries.[13]

Despite great effort, examples of disappointment in global health are still too easy to find. Diarrheal diseases and respiratory infections are the leading communicable disease killers for children under five. However, while there has been a substantial decline in diarrheal mortality in recent years, child deaths from respiratory infections remain high and are projected to decline only very slowly.[14] The proportion of children under five with upper respiratory tract infections being treated with antibiotics rose from 42 percent to 71 percent globally from 1998, but only 35 percent of those children were treated according to clinical guidelines in the period surveyed.[15] Countries have repeatedly changed their standard treatment guidelines for malaria because of unacceptable levels of resistance to older drugs, and yet African households with young children are far more likely to use older drugs than new, effective ones.[16] These connections between inappropriate drug use and poor health outcomes do not provide iron-clad proof of drug resistance as a cause, but point to it as a factor, suggesting that progress in childhood disease reduction will be difficult unless drug efficacy is improved and new drugs are carefully stewarded to prolong their therapeutic value.

Still more worrisome is that resistance to one type of drug for treatment of one disease affects the ability to treat other diseases. Concerns about antibiotic longevity are particularly acute. Two-thirds of antibiotics in the world are sold without prescription, and the pipeline for new antibiotics is nearly dry. Indeed, antibiotics are the cornerstone of health care—as essential to successful surgery, reproductive health, and other health needs as they are to treating diseases.

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

Figure 1.2
Documented examples of drug resistance by disease



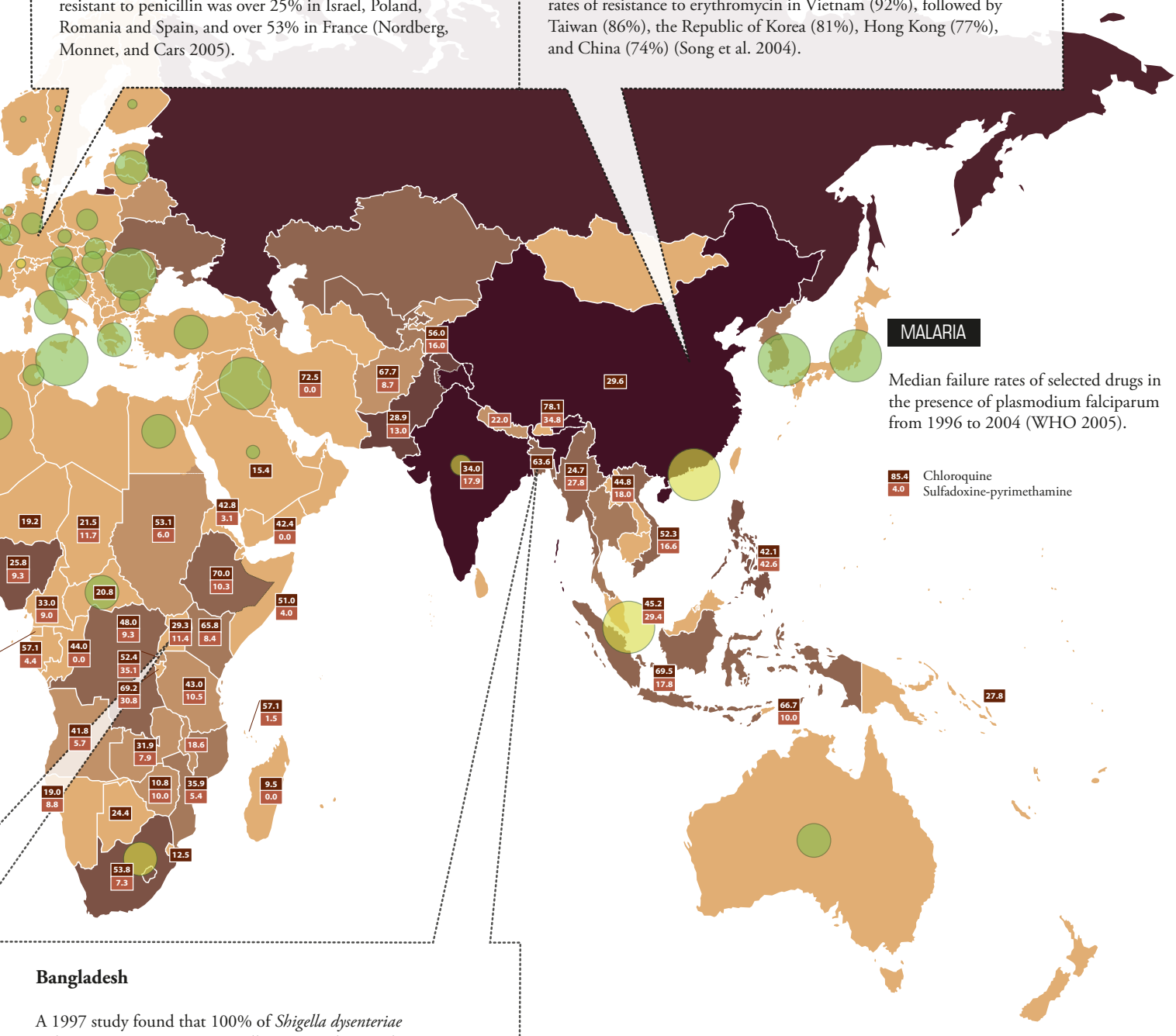
PNEUMONIA

Europe

In Europe in 2002, the proportion of *S. pneumoniae* isolates resistant to penicillin was over 25% in Israel, Poland, Romania and Spain, and over 53% in France (Nordberg, Monnet, and Cars 2005).

East Asia

S. 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%) (Song et al. 2004).



MALARIA

Median failure rates of selected drugs in the presence of plasmodium falciparum from 1996 to 2004 (WHO 2005).

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; 93% were resistant to ampicillin, tetracycline, chloramphenicol, TMP-SMX, and nalidixic acid (Jahan and Hossain 1997).

In the common drivers of resistance shared by diseases lie the greatest potential solutions

For example, doxycycline is used to treat multiple bacterial and parasitic diseases. The result is increased selection pressure for resistance of multiple infectious agents, and reduced therapeutic efficacy across diseases.[17] Underscoring the need to monitor drug efficacy across diseases is the rapid rise in the number of people co-infected with pathogens that cause more than one disease, notably TB and HIV/AIDS.[18]

Several examples illustrate the complexities of drug interactions across diseases.

- There is evidence of increased carriage of cotrimoxazole-resistant strains of *S. pneumoniae* in children after they have been treated with Sulfadoxine-Pyrimethamine (SP) for malaria.[19]
- Heavy use of chloroquine to treat malaria appears to select for ciprofloxacin resistance in *Escherichia coli*.[20]
- Rifampin use for TB treatment severely limits treatment options for HIV/AIDS by lowering anti-HIV protease inhibitor concentrations (through cytochrome oxidase inhibition).[21]

Economic consequences

Drug-resistant forms of disease create financial and economic costs for the patient and the health system. There is a huge price premium for second- and third-line drugs used to treat resistant disease. In Brazil, for example, a large share of the Health Ministry budget pays for second-line antiretrovirals.[22] Further, more health resources are needed to treat resistant forms of diseases, such as medical personnel, hospital beds, testing kits, and other supplies. And patients with resistant forms of infection spend a substantially longer time in the hospital and under treatment.

The opportunity costs of treating resistant disease are also considerable. It costs as much to cure one patient of extensively drug-resistant tuberculosis (XDR-TB)[iv] as it does to cure 200 patients of susceptible TB. Society therefore has good economic reason to look for ways to slow, reduce, and contain resistance. Finally, donors have been forced to divert funds to pay for more expensive drugs, but their financial efforts are not reaching even a fraction of the people who contract resistant forms of disease and will probably become unsustainable as the patient burden grows.

iv. 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.

Many commonalities among resistance drivers

Drug resistance is a complex biological phenomenon with myriad interacting factors, both naturally occurring and human-made, that determine its emergence and transmission. Variations in how pathogens develop resistance derive from different biological modes of action between and among types of bacteria, viruses, fungi, and parasites and the various drugs they interact with. There are no standard ways to define mechanisms of resistance across organisms—making measurement of drug resistance difficult. Specific disease characteristics also affect the processes through which resistance arises and how much it alters therapeutic options. Differences in resistance patterns stem as well from the choices that governments, health-care providers, and patients make.

There are many drivers of resistance and an equal number of ways to slow, reduce, or contain it. 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:

- Missing and inadequate technology
- Manufacturer, prescriber, dispenser, and patient behavior that leads to inappropriate drug use
- Weak health systems with limited laboratory capacities and public surveillance
- Poor-quality and counterfeit drugs with the wrong level of active therapeutic ingredients
- Excessive use of antibiotics in agriculture.

These drivers are similar across diseases, yet, where it is currently being addressed, resistance is primarily being tackled vertically, disease by disease, through small-scale and uncoordinated efforts. Tackling the drivers systematically in order to slow resistance is a global responsibility—we must not let the global social good of drug treatment be undone by lack of awareness and indifference. Box 1.1 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.

We can slow drug resistance

Many of the conditions accelerating drug resistance can be fixed, and the spread of resistance can be greatly slowed. The needed

Box 1.1
A framework for the Drug Resistance Working Group: 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 nonrenewable resource for which there is an optimal rate of depletion.[1] 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 (our willingness to save the resource for later use). In simple terms, because resistance occurs naturally, there is a temporal trade-off to consider: Do we use drugs to treat infections now or save them for later?

Complicating that decision is inappropriate drug use, which hastens the evolutionary process. Thus, the question becomes: Can you use the drug correctly now, and maintain the ability to use it in the future? One person's misuse of a drug has negative consequences for others by helping to select and spread resistant strains, thereby decreasing the probability of others being cured. Indeed, misuse of a drug stands a good chance of impeding the user's own health. Both these factors illustrate that drug efficacy has social value that must be recognized and protected through policy interventions and appropriate institutional arrangements to manage the scarce resource responsibly. It is a potent example of the "Tragedy of the Commons."

The Working Group's recommendations encourage actions that help to balance society's current and future health care needs and to 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. Providing good information in a timely manner creates the conditions for better informed decisions by drug and diagnostic manufacturers, major drug purchasers, distributors, prescribers, dispensers, 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.

1. See http://www.sciencemag.org/cgi/content/full/162/3859/1243.

Source: Laxminarayan (2002); Outterson, (2005).

fixes will be more effective if they are applied across diseases. This approach is consistent with the recent attention from donors and technical agencies to strengthen health systems.[23] Resistance can be prevented and contained if the following actions are pursued.

- **Know the problem:** a common foundation of better information about drug quality and resistance, including improved surveillance, diagnosis, and laboratory capacity
- **Own the problem:** stronger global and national regulatory and policy leadership and enforcement
- **Develop new technologies:** strengthened pipelines for new drugs and other technology
- **Use existing products better:** proper distribution, marketing, prescribing, dispensing, and use of drugs and diagnostics.

Slowing drug resistance will require the commitment and action of multiple public and private actors. Table 1.1 summarizes the responsibilities of key actors in ensuring drug resistance is managed and controlled with society's benefit in mind.

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.[24] A crucial contribution to sustaining the benefits of current drugs is the continued investment in vaccine research and development.[25] Donors are also working closely with each other and with national health authorities to strengthen health systems in developing countries. These efforts are to be applauded and encouraged, and while some donors have taken active steps to tackle resistance, these steps need to be amplified by stronger measures to protect and monitor 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.

Governments have a responsibility to provide regulation and oversight of drug and diagnostic licensing, manufacturing, quality, and use. Governments are also the primary providers of public health surveillance to detect and monitor when drugs are no longer effective, and significant providers of laboratories for testing drug sensitivity and diagnosing disease. International technical, financial, and law enforcement agencies have a role to play in providing information and guidance, coordination, financial resources, and assistance in protecting drug quality at the country level.

Critical among the responsible actors 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.

Last, but perhaps most important, are the **health care providers** with direct access to patients, whose decisions and those of the patients they treat ultimately determine the rate and manner in which drug resistance develops and spreads. They need the tools, knowledge, authority, and incentives to make diagnosis and treatment decisions that benefit their patients and themselves, while minimizing the harm to others—now and in the future.

The goal of this report is to focus attention on solutions designed to improve incentives to reduce drug resistance, to increase 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 and spread 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.

Table 1.1
Responsibilities of key actors

Actor	Role
Global health donors	Support health improvements including effective treatment options, information systems, R&D incentives
National governments	Regulate and oversee drug supply, enforce laws, maintain functioning health systems, including drug testing and resistance surveillance, support R&D efforts
Drug and diagnostic manufacturers	Ensure products are safe and effective
Health care providers and patients	Share and use relevant information about drug quality and efficacy, adhere to protocols and treatment guidance, advocate for policies to improve quality of care by containing drug resistance

Notes

1. Walker et al. (2009).
2. Communication from the Global Fund, April 2010; PEPFAR (2010); UNITAID (2009).
3. Gonzales et al. (2008).
4. WHO (2008a).
5. Dondorp et al. (2009).
6. Patrick and Hutchinson (2009).
7. Hyde et al. (2001).
8. Bennett (2010).
9. WHO (2008c).
10. http://www.stoptb.org/gdf/.
11. Infectious Disease Society of America (2010).

12. Borgdorff and Small (2009).
13. Gonzalez (2008).
14. WHO (2008b.)
15. WHO (2009b).
16. WHO (2004a); Macro International, Inc. (2009).
17. Feikin et al. (2008); Davidson et al. (2008).
18. von Gottberg et al. (2008); Davidson et al. (2008).
19. Feikin et al. (2008).
20. Davidson et al. (2008).
21. http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/PDF/tbhiv.pdf.
22. Sabot, Clinton Health Access Initiative, Personal communication, April 12, 2010.
23. Frenk (2010).
24. http://www.pepfar.gov/about/c19388.htm; http://www.theglobalfund.org/en/distributionfunding/?lang=en; UNITAID (2008).
25. Okeke (2009).

2
Health and economic consequences of the global drug resistance problem

Chapter at a glance

- The growing need to use second- and third-line drugs to treat AIDS, TB, and malaria, as well as other prominent developing country diseases, challenges gains in improved drug access and health outcomes.
- Many antibiotics either have lost or quickly are losing their effectiveness, resulting in profound long-term health and economic consequences. Children, who are especially vulnerable to infectious diseases, often bear the brunt of antibiotic resistance.
- Drug-resistant TB is spreading rapidly to countries where it has not been seen before, leading to an increased number of deaths.
- The frequent mutations of HIV imply that all patients on antiretroviral therapy will eventually acquire resistance to their therapy. Donors and governments will increasingly face higher costs of second-line drugs for HIV/AIDS patients.
- Annually, malaria kills almost 1 million children under the age of five in sub-Saharan Africa. Artemisinin-based combination therapies, the newest and most effective malaria drugs, are already showing signs of lower efficacy.

Only a fraction of childhood pneumonia strains remain treatable with penicillin

Khalifa's Story

Meet Khalifa,[i] a nurse who works in the outpatient clinic of Apam Catholic Hospital serving Gomoa district, Ghana. Gomoa has a population of just over 200,000 people and is a long car ride from the capital city, Accra. Although it is always busy—the hospital sees more than 100 outpatients a day—Khalifa loves her work. Except that recently, it has not been easy. A few months ago, she started having headaches and then stomach aches. She felt feverish. In the evenings she felt cold. These are typical symptoms of malaria. So she took malaria treatment. *(continued in chapter 3)*

What are the health consequences of resistance?

This section reviews what is known about the prevalence of drug resistance and how it affects the ability to cure the major diseases of developing countries. Our knowledge of drug resistance is especially limited for those diseases that primarily affect children, such as pneumonia, diarrhea, and malaria which collectively account for 41 percent of under-five deaths.[1] Global drug resistance monitoring databases or networks exist or are being developed for HIV/AIDS, TB, and malaria—largely due to the pre-eminence of those diseases in donor programs. Although the existing efforts are piecemeal relative to the full extent of drug resistance globally, they go far beyond any systematically collected data for antimicrobial resistance (AMR).[ii] There is no mechanism or institution that currently collects or analyzes resistance across diseases and looks for links from one type of resistance to another. Chapter 4 has more detail on existing efforts to monitor drug resistance and what they lack to support an effective public health and clinical response. Appendix B shows the historical picture of drug introductions and emergence of resistance to the drugs that treat the diseases highlighted in this report.

Bacterial pathogens

Knowledge of antibiotic resistance prevalence in developing countries is extremely limited. What we know comes primarily from small-scale studies by academic and other research or advocacy organizations such as the Alliance for the Prudent Use of Antibiotics (APUA)[iii] and the International Network for the Rational Use of Drugs, which document local pathogen-specific resistance problems. Larger-scale resistance monitoring programs have not been sustained.[iv] The existing studies all point to one conclusion: Most antibiotics are quickly losing their effectiveness. Here we highlight two of the most lethal infections that children in the developing world experience and the implications of resistance for curing them.

S. pneumoniae causes high levels of morbidity and mortality among children worldwide, particularly in developing countries.[2] An estimated 10.6 million children under five experience some form of pneumococcal infection every year, and 1.6 million die from pneumonia.[3] For many years, these infections were cheaply cured with penicillin, one of the world's first antibiotics. Now, penicillin effectively treats only one-half to two-thirds of the *S. pneumoniae* strains circulating in many developed and developing countries, and less than one-quarter of strains in certain regions. Penicillin-resistant strains are also more likely to be resistant to other antibiotics.[4] Multi-drug-resistant *S. pneumoniae* clones that are resistant to penicillin and three other common antibiotics[v] are thought to be widespread and predominant in Hong Kong, Japan, and Singapore.[5]

An extremely contagious and often lethal diarrheal pathogen, the bacterial *Shigella* genus, is responsible for up to 600,000 (mostly child) deaths every year.[6] All four species (*dysenteriae*, *flexneri*, *boydii*, and *sonnei*) of *Shigella* have exhibited resistance to antibiotics, which are recommended for bacterial diarrhea.[7] Where surveillance has been systematic, in Latin America for example, very high rates of resistance are found (see figure 2.1). Less than

i. Khalifa is featured in a short film that accompanies this report, entitled *The Race Against Drug Resistance,* which can be found at www.WhenMedicinesFail.org. She tells her story through the film. An adapted version appears in this report.

ii. Where antimicrobial resistance means the 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)

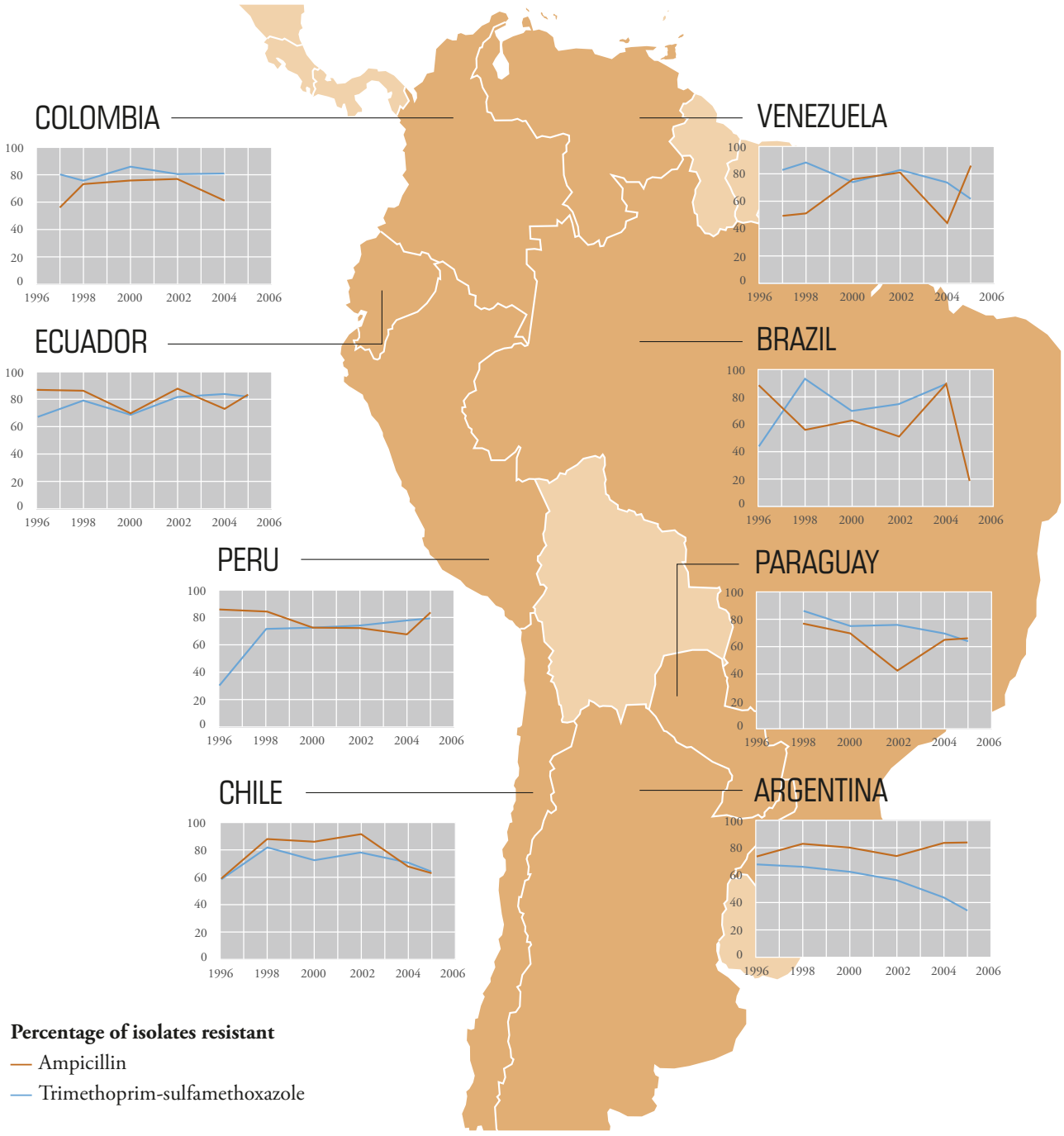
iii. The APUA network of affiliated chapters in 60 countries, including 30 in the developing world, support country-based activities to control and monitor antibiotic resistance tailored to local needs and customs.

iv. For example, The Alexander Project was an international, industry-sponsored surveillance program on community-acquired respiratory pathogens, such as *S. pneumoniae*. It existed from 1992 to 2002.

v. Chloramphenicol, tetracycline, and erythromycin.

Most antibiotics are quickly losing their effectiveness

Figure 2.1
Prevalence of drug-resistant strains of *Shigella*, selected countries in Latin America



Note: Sample sizes vary by country and year.

Source: Graphic adapted from figures published in Zurita (2008).

In Africa, only six countries were able to contribute data to the 2008 global report on TB drug resistance

Table 2.1
Cumulative mortality during treatment for XDR-TB, MDR-TB, and drug-susceptible (DS)-TB cases—United States, 1993–2006

Time period	DS-TB cases (percent)	MDR-TB (percent)	XDR-TB (percent)
Month 0–5	9	14	18
Month 6–11	10	19	24
Month 12–23	10	23	27
Month 24–35	11	23	28
Month 36+	11	26	35

*Limited to cases alive at diagnosis, initially treated with one or more TB drugs, with both start and end dates reported. The percentage is cumulative mortality.

Source: Shah et al. (2008).

40 percent of *Shigella flexneri* isolates in most Latin American countries are sensitive to cheap and relatively safe antibiotics.[vi] The clinical implications are that these drugs can no longer be used for empiric treatment of dysentery. Data from Asia paint a similar picture of high resistance of *Shigella* to trimethoprim-sulfamethoxazole (81 percent), tetracycline (74 percent), and ampicillin (53 percent) and, worryingly, increasing rates of resistance to ceftriaxone (5 percent) as well as to the current WHO recommended treatment for shigellosis, ciprofloxacin (10 percent).[8]

Tuberculosis

Resistance to the drugs used to treat TB is clearer. Annually, approximately 3.6 percent of all incident TB cases result from a multi-drug-resistant strain and, in 2008, an estimated 440,000 new MDR-TB cases emerged, resulting in approximately 150,000 deaths.[9] By the end of 2008, 58 countries had reported at least one case of XDR-TB and 5.4 percent of all MDR-TB cases were XDR-TB.[10] Unfortunately, a very large proportion of TB cases caused by a resistant strain go undetected and, even among those cases that are detected, many remain untreated. In 2008 only 7 percent—or 29,423 cases—of all MDR-TB cases that are estimated to have emerged during that year were reported.[11]

Furthermore, while there are no precise estimates available on the number of XDR-TB cases globally, limited evidence suggests that there may be around 25,000 per year and that most cases are unrecognized and fatal.[12]

The health consequences of a drug-resistant TB infection are severe. Table 2.1 compares the likelihood of death from drug-susceptible and drug-resistant TB after different intervals of treatment. In the United States, when WHO guidelines are followed, about 26 percent of MDR-TB cases die from the illness after three years.[13] For XDR-TB, mortality rises to about 35 percent. However, mortality rates may be considerably higher in other countries: For example, evidence from the Republic of Korea suggests that XDR-TB mortality rates can be as high as 71 percent.[14] In the Philippines, 61 percent of patients in one study were cured—at a cost of more than US$4,000 per patient.[15]

TB is one of the most common opportunistic infections affecting HIV-positive individuals. As many as one-quarter of deaths attributed to TB are in patients co-infected with HIV.[16] People living with HIV and AIDS are far more likely to die from MDR-TB or XDR-TB than those who do not have HIV infection—some studies show case fatality rates of 90 percent.[17] Data gaps remain, however. In Africa, which has the highest TB incidence of all regions in the world, only six countries were able to contribute data to the 2008 global report on TB drug resistance.[18]

vi. Ampicillin, trimethoprim/sulfamethoxazole (SXT), and ciprofloxacin.

In 2010, only one African country, Mozambique, was able to provide information on TB drug resistance among HIV-positive populations.[19] The lack of data has made it impossible to conclude whether there is a definite overall association between the HIV and MDR-TB epidemics.[vii,20]

HIV/AIDS

Developing country antiretroviral therapy (ART) resistance data are extremely sparse and do not yet allow for disaggregation by subpopulation or specific risk factors. However, a lack of data does not mean that ART resistance is not or will not be a problem. The association between ART use and HIV drug resistance exists on a global level.[21] Time will be the enemy of ART drug efficacy as all patients on ART can expect to eventually develop a virus with acquired resistance. Unfortunately, the global health discourse about extending use of antiretrovirals (ARVs) focuses almost exclusively on treatment targets, neglecting the reality that as more drugs are used, more resistance will be selected for. Thus, other aspects of care, including adherence, monitoring of response, and systematic surveillance for resistance, are critical.

Evidence from developed countries, where ART has been available for a considerably longer time than in developing countries, is ominous. A recent review found transmitted ART resistance levels (cases in which people were infected with an already resistant strain of HIV) of 11.4 percent in North America and 10.6 percent in Europe.[22] A study in the United Kingdom concluded that 28 percent of patients starting currently recommended first-line regimens in routine clinical practice showed virological failure, and 17 percent had a drug-resistant form of the virus.[23] High resistance levels in industrialized countries are partly a reflection of the use of ART monotherapy before the development of combination therapy. HIV mutates at an extremely high rate, and the emergence of resistance in an individual on treatment is easily exacerbated by suboptimal drug adherence, a common problem observed in the treatment of chronic illness where drug therapy is lifelong and carries potential side effects or toxicities. Indeed, in the presence of suboptimal drug levels, a drug-resistant HIV strain can become the predominant circulating strain within an individual in two to four weeks.[24]

Studies from the Global HIV Drug Resistance Surveillance Network[viii] find little evidence in developing countries of rapid transmission of drug-resistant HIV strains among samples tested. 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] Relatively low levels of transmitted resistance may be partly explained by the fact that drug-sensitive HIV has a greater capacity to replicate and be transmitted than most drug-resistant strains.[26] However, to date it has been difficult to separate base levels of naturally occurring resistance from transmitted resistance. The former doesn't appear to prevent ARVs from working, whereas the latter does.[27] Regular resistance monitoring over time to understand better transmission of resistant strains of HIV is hence critical.

Detection of *in vitro* ART resistance by standard genotyping methods is expensive, not routinely available, and rarely done in developing countries. Furthermore, viral load monitoring is not common practice in treatment programs in resource-limited settings, suggesting that resistance may emerge in patients who continue to receive therapy while also on nonsuppressive regimens.[28] A database to monitor and analyze resistance to subtype-C sequences, the virus common in Africa, is under development.[29]

Malaria

More than 40 percent of children worldwide live in malaria-endemic countries.[30] Annually, malaria kills almost 1 million children under the age of five in sub-Saharan Africa alone.[31] The long-term effects of malaria on a child's health and development are often insufficiently recognized and poorly managed.[32] A severe form of the disease, cerebral malaria, kills 10–20 percent of those children it affects, while an additional 7 percent are left with permanent neurological problems, including blindness, epilepsy, and speech and learning difficulties.[33]

Chloroquine was an effective first-line malaria treatment for more than 50 years, but when resistance rates became unacceptably high in the mid-1990s, SP became the only affordable, effective alternative with limited side effects. Parasites resistant to SP

vii. There is a clear and definite association in Latvia (nationwide survey) and Donetsk Oblast, Ukraine (whole oblast). The causative pathway of that association is not clear but includes previous treatment and history of imprisonment. (Personal communication, Paul Nunn, Stop TB program, WHO, May 12, 2010.)

viii. A program developed by WHO in collaboration with the International AIDS Society.

emerged almost immediately; resistance was first documented the same year the drug was introduced. The global malaria community breathed a sigh of relief when artemisinin-based combination therapies (ACTs) became widely available over the past decade. Relief was short-lived. The efficacy of artesunate monotherapy has declined relatively widely, and ACTs are showing signs of lower efficacy along the Thai-Cambodian border, which causes an alarming case of déjà vu, given that chloroquine resistance originated in South East Asia before spreading to the rest of the world.[34]

Hospital-acquired infections

Of the approximately 2 billion individuals carrying the bacterium *S. aureus* globally, it is estimated that between 2 million and 53 million carry an increasingly common multi-drug-resistant form: methicillin-resistant *S. aureus* (MRSA).[35] In the United States, MRSA kills about 18,000 people annually. While MRSA is primarily hospital-acquired, it now appears as a community-acquired infection outside the hospital as well.[36] As with TB, other resistant infections are increasingly found to emerge and spread within and between hospitals or clinics and the community. The 2007 MDR-TB and XDR-TB outbreak in the rural South African community of Tugela Ferry is a case where transmission of MDR-TB and XDR-TB took place both in clinics and in communities.[37]

What are the economic consequences of resistance?

There are important societal consequences of resistance beyond health. Resistance to first-line drugs has a startling impact on the cost of curing patients. In many countries, expenditures for drugs represent a large proportion of overall health-care costs, ranging from 20 to 60 percent of total expenditure on health in poor countries.[38] Slowly but surely, the growing need for second- and third-line drugs to treat AIDS, TB, and malaria, as well as diseases caused by common developing country pathogens such as *S. pneumoniae* and *Shigella,* are challenging recent gains in drug treatment. This 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 issue from a broader societal perspective, including that of donors that are trying to achieve maximum health impact from their investments.

Second-line drugs cost more

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 to treat developing country diseases, and increased generic competition for some products, prices of many first-line drugs have fallen dramatically in recent years. But the prices of newer and on-patent drugs—and that means most second- and third-line drugs—are still far higher, and are paid by patients directly or by donors and governments on behalf of patients. Patients are placed on specific drugs for different reasons, and what is first-line at one time and place can change, depending on the patient, ecological conditions, and drug availability. Nonetheless, in broad terms, 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, country governments and donors face greater challenges in meeting treatment targets and health-care providers face excruciating choices about who receives which treatment.

The international drug market is complex, particularly where a market is segmented by multiple buyers and payers. 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. Donor payments for ARVs, anti-TB drugs, and—with a new global subsidy for ACTs called Affordable Medicines Facility-malaria (AMFm) currently in a pilot phase—malaria drugs provide greater access to and cheaper or free drugs in the short term (see box 4.6 for detail). But subsidization cannot continue indefinitely. The AMFm, in particular, is well designed to reach consumers far beyond the limited number that come to public clinics, but it remains uncertain whether it can reach enough patients in developing countries who need these treatments to slow the spread of resistance to artemisinin.

Antiretroviral drugs

AIDS advocacy groups have successfully urged greater transparency in ARV pricing. As a result, greater information about ARV prices and trends is available than for other drugs. First-line ARV prices have moved downward over the past five years, but there is a persistent large gap between prices of first- and second-line ARVs. The small percentage of patients on second-line drugs

The economic cost of drug resistance in developing countries is not readily measured

Table 2.2
Comparison of first- and second-line ARV prices

Average first-line price (USD)	Average second-line price (USD)	Difference between second-line and first-line prices
$90/patient/year	$1,214/patient/year Third-party negotiated: $425/patient/year	Average: 14-fold Donor-negotiated: 5-fold

Note: Median prices of first- and second-line highly active antiretroviral therapy in low-income countries in 2007. Higher prices prevail in middle-income countries. Lower price shown is available in a defined set of developing countries through agreements with the Clinton Health Access Initiative.
Source: Waning et al. (2009) and AIDS2031 (2009).

accounts for nearly 20 percent of total ARV expenditures because of the high cost of second-line drugs compared to first-line drugs.[39] Table 2.2 illustrates that gap.

In 2007, prices of second-line ARV treatment were at least 9 times and up to 17 times more than the prices of first-line treatment on a per-patient annual basis (depending on access to generics).[40] This disparity has begun to decline in countries with access to generics, and will likely continue to fall as the number of patients experiencing drug resistance increases (thereby leading to greater economies of scale in producing second-line drugs). In 2009 the Clinton Health Access Initiative signed an agreement with Matrix Laboratories to offer a once-daily four-drug regimen for second-line treatment of HIV/AIDS at a price of US$425 annually starting in 2010, 28 percent lower than the previous lowest-priced alternative.[ix,41]

There were more than 3 million patients on ARVs across the developing world at the end of 2008, and between 200,000 and 250,000 patients on second-line therapy.[42] The percentages requiring second- and third-line drugs will grow steadily in the coming years as more and more HIV/AIDS patients experience first-line treatment failure or poor reactions to first-line drugs. Although it is not possible to know the precise reasons, about 22 percent of AIDS patients switch to second-line therapy after an average of 20 months on first-line therapy,[43] and health care experts expect that high mutation rates of the virus mean that eventually all those on ART will acquire resistance to the drugs they take.

Tuberculosis drugs

All first-line TB drugs are decades old and thus off-patent and widely available in the public and private sectors, though they vary in price across countries and types of health providers.[44] There are currently only six classes of 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.[45] WHO's Stop TB program sponsors the Global Drug Facility, which provides second-line TB therapy to patients through public clinics for about US$3,500 per course.[x] Table 2.3 shows the average prices of first- and second-line TB drugs. A large share of the financing for second-line TB drugs comes from UNITAID, which is funded by donors.

Malaria drugs

The most common drugs to which there is widespread resistance in Africa, chloroquine and SP, are priced at well under US$1 per course, though prices vary across countries and providers. Artemisinin monotherapy costs between US$1 and US$2 (table 2.4). Because of high levels of parasite resistance to those drugs, the only WHO-recommended treatment for malaria is ACT. However, earlier-generation drugs are widely available and

ix. This price is available to any member of the Clinton Health Access Initiative's Procurement Consortium—which includes over 70 low- and middle-income countries—that is able to access generics.

x. Country-based anti-TB programs must be approved by WHO to receive second-line drugs through the Green Light Committee.

Table 2.3
Comparison of first- and second-line anti-TB drug prices

Average first-line price (US$)	Average second-line price (US$)	Difference between second-line and first-line prices
$20/course	$3,500/course	175-fold

Source: Data for 2009 Global Drug Facility supplies, Stop TB Partnership.

Table 2.4
Comparison of earlier-generation and current antimalarial prices

Average early-generation and monotherapy prices (US$)	Average recommended treatment price (US$)	Difference between second-line and first-line prices
$0.05–$0.25/adult course (chloroquine/ SP) $1.50/adult course for artemisinin monotherapy	Private: $5–$10/adult course (ACT) Donor-funded: $0.20–$0.50 in private settings, free or $0.05 in public settings	Private: 3- to 500-fold Public: rough equivalence

Sources: Laxminarayan and Gellband (2009) and MSH International Drug Price Indicator Guide (2008); Oliver Sabot, Clinton Health Access Initiative, personal communication, April 2010.

commonly used in developing countries. Currently, subsidized ACTs are being made available through the Clinton Foundation and donors at about twice the price of the old drugs, but unsubsidized ACTs retail for 20 to 40 times as much and their availability across different settings varies significantly. Where available through a public clinic, ACTs are generally free to patients.[46]

Antibiotics

There is no simple way to analyze the price differences among first- through fourth-line antibiotics because of huge variability across countries. However, one can relatively easily examine the price differences between new and older antibiotics in one country, recognizing that newer drugs are often reserved for emergency conditions, and older drugs that have been less widely used can still be very effective. As an example, the prices for several older antibiotics are presented in table 2.5, adjacent to the prices for newer antibiotics. The price difference on a per-dose basis ranges from 2 to 60 times more for the second-line drugs, although the total cost depends on the length of the treatment course.

Donor costs of treating resistant forms of disease

Although across developing countries roughly 70 percent of pharmaceuticals are purchased by households,[47] a significant share of drug costs in the lowest-income countries is borne by external funders. Many have spent considerable money and effort to reduce the prices and increase the availability of essential drugs.

More than US$2 billion is being invested annually in increasing access to key drugs for HIV, TB, and malaria through the Global Fund to Fight AIDS, Tuberculosis and Malaria and the U.S. President's Emergency Plan for AIDS Relief alone.[48] Other major institutions that channel large sums to purchase drugs for developing countries are UNITAID, WHO, the United Nations Children's Fund (UNICEF), bilateral government programs, nongovernmental organizations (NGOs), and private organizations. Relatively little donor funding appears to be allocated specifically to antibiotics for childhood and other infections common in developing countries.

The Global Fund to Fight AIDS, Tuberculosis and Malaria allocates 45 to 50 percent of its outlays on drugs and other

Table 2.5
Comparison of sample first- and second-line antibiotic procurement prices in Uganda

Average first-line price (US$)	Average second-line price (US$)	Difference between second-line and first-line prices
$0.14 per tab-cap (ciprofloxacin 500 mg.) $0.01 per tab-cap (penicillin v. 250 mg.)	$0.26 per tab-cap (amoxicillin/ clavulanic acid 250 mg.) $0.62 per vial (ceftriaxone 1 g.)	2- to 60-fold

Note: The final price to the patient is composed of the manufacturer's selling price plus taxes, tariffs, markups, and other supply chain costs. See http://www.haiweb.org/medicineprices/ for discussion of what retail medicine prices include.

Source: MSH International Drug Price Indicator Guide (2008) and JMS price guide (2009).

Table 2.6
Major donor purchases of second- and third-line drugs for developing countries

UNITAID	2006–2008 2007–2011	US$45 million for second-line ARVs US$65 million for ACT scale-up
Global Drug Facility/ Stop TB Partnership	2008–2011	US$34 million planned for MDR-TB scale-up
Roll Back Malaria	2006	100 million doses of ACTs procured
Global Fund to Fight AIDS, Tuberculosis and Malaria	2009–2014	US$325 million committed US$1.5 to US$1.9 billion estimated for ACT subsidy

Source: Organization Web sites as of March 2010.

commodities to treat priority diseases; first-line drugs constitute most of its allocations.[49] However, an unintended consequence of greater drug access and use is greater selective pressure on pathogens, which leads to the development and spread of resistant forms of disease. As shown in table 2.6, donor organizations are increasingly purchasing substantial quantities of second- and third-line drugs. The available information is not comprehensive with regard to donor funding for second- and third-line drugs, nor does it include antibiotic purchases supported by donors nor the outlays by country ministries for drugs to treat resistant infections. However, it is undeniable that the additional expense to donors of providing treatment for patients with drug-resistant strains will pose an increasing challenge as donor budgets become tighter and greater emphasis is placed on prevention and other health system needs.

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 monitoring and reporting burdens. Further direct costs to health systems include the time of medical professionals, bed space,

Table 2.7
Drug-resistance national costs from selected studies in the U.S. and E.U.

Site of study	Type of resistant pathogen	Costs (USD)	Author, year
E.U., plus Norway and Iceland	Four types of resistant bacteria, including both gram-positive and gram-negative	$2.2 billion in 2007 Direct hospital costs, $1.4 billion; direct outpatient costs, $14 million; indirect costs, $200 million; indirect costs from lost life years $600 million	EMEA (2009)
E.U., U.S.	*P. aeruginosa* infection	$2.7 billion Direct and indirect costs	Spellberg et al. (2007)
E.U., U.S.	*S. aureus*	$14.5 billion in 2003 (2004 $) Direct costs from hospital stays only	Noskin et al. (2007)
U.S.	Resistant infections in hospital inpatients	Incremental costs of $18,588–$29,069 per patient; extrapolates to $16.6 to $26 billion nationwide	Roberts et al. (2009)
U.S.	Hospital-acquired sepsis and pneumonia, including MRSA	$8.1 billion (2006)	Eber et al. (2010)

and hospitalization for patients with resistant infections. All of the costs above are likely to be borne by developing country governments or by national health-insurance schemes where they exist. Okeke et al. (2005) detail other costs associated with treating resistant diseases.[50]

Costs of resistance to regulatory and policy systems include updates and changes to guidelines and their implementation and drug quality inspection and enforcement. Lack of information about resistance and lack of capacity to respond mean that guideline updates, inspections, and enforcement happen only rarely.

Smith et al. (2005) argue that drug resistance imposes costs on society beyond the direct health-related aspects, including effects on nonhealth sector and macroeconomic indicators, such as labor supply and economic growth.[51] Broad costs to society include the human losses involved in extended periods of illness and the higher risk of premature death from difficult-to-treat or untreatable diseases. More often than not, when resistance is present in a community or health care setting, the additional services listed above are not provided, the staff is not trained, the health system capacity is not available, and the costs are absorbed by unknowing patients. For treatment of malaria and bacterial infections, in particular, where treatment often occurs outside the mainstream health system and beyond the support of governments and donors, the costs of drug resistance are borne directly by the patient, often in failed efforts to cure an illness, with death the frequent result.

The economic cost of drug resistance in developing countries is not readily measured. It is complicated by a lack of data, including difficulty discerning in a clinical setting the reason for switching a patient's drug regime amidst the many constraints on treatment decisions. Yet, sufficient data may be available for

preliminary estimates to be made using data from national TB programs, WHONET,[xi] and APUA.

Estimates of the full costs of drug resistance have been made in developed countries on a limited number of resistant bacteria and settings. Because of growing health and economic concerns, the E.U. has begun to systematically measure the costs of infections caused by drug-resistant pathogens.[xii] Table 2.7 provides recent estimates from the United States and the European Union. Although they pose serious concerns for the countries affected, the estimates do not provide insights into drug-resistance costs in developing countries. We recommend specific research and analysis on developing country social and economic costs of drug resistance in appendix A.

Notes

1. Gonzales et al. (2008); Black et al. (2010).
2. Scott (2008); Plotkin, Orenstein, and Offit (2008).
3. Black, Morris, and Bryce (2003).
4. Nugent, Pickett, and Back (2008).
5. Jacobs et al. (2003).
6. Kotloff et al. (1999).
7. Okeke et al. (2005).
8. Kuo et al. (2008).
9. WHO (2010).
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12. Raviglione and Zignol (2010).
13. Shah et al. (2008); WHO (2009a).
14. Kim et al. (2010).
15. Tupasi et al. (2006).
16. WHO (2009a).
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19. Matteo Zignol, Stop TB Partnership. Personal communication, March 31, 2010.
20. WHO (2010).
21. Bennett (2010).
22. Maglione et al. (2007).
23. Harrigan (2010).
24. Bennett (2010).
25. Bennett et al. (2008); Ndembi et al. (2008).
26. Bangsberg et al. (2006).
27. Blanco et al. (2010).
28. Ford, Mills, and Calmy (2009); http://www.medscape.com/viewarticle/498359.
29. de Oliveira, Shafer, and Seebregts (2010).
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32. http://www.rollbackmalaria.org/cmc_upload/0/000/015/367/RBMInfosheet_6.htm, accessed March 28, 2010.
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34. Dondorp et al. (2009); Alker et al. (2007); Denis, Tsuyuoka, Poravuth et al. (2006); Denis, Tsuyuoka, Lim, et al. (2006); Noedl et al. (2008).
35. Grundmann et al. (2006).
36. Tacconelli et al. (2008); Muto et al. (2003).
37. Ghandi et al. (2006).
38. WHO (2004b).
39. Waning et al. (2009).
40. WHO (2007).
41. Clinton Foundation, August 9, 2009.
42. Waning et al. (2009).
43. Keiser et al. (2009). Cited in AIDS2031 (2009).
44. Laing and McGoldrick (2000).
45. For lower estimate, see http://www.who.int/tb/features_archive/drs_factsheet.pdf. For higher estimate, see Tupasi et al. (2006).
46. MMV (2008).
47. WHO (2004b).
48. Estimated from PEPFAR and Global Fund expenditures at: http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=28441. Accessed December 4, 2008.
49. The Global Fund, Pre-Board Briefing, May 9, 2009.
50. Okeke et al. (2005).
51. Smith et al. (2005).

xi. WHONET is a free Windows-based database software developed for the management and analysis of microbiology laboratory data with a special focus on the analysis of antimicrobial susceptibility test results. The software has been developed since 1989 by the WHO Collaborating Centre for Surveillance of Antimicrobial Resistance.

xii. See http://www.eu-burden.info/.

3
Drivers of drug resistance

Chapter at a glance

- The major drivers of drug resistance include a vexing mix of technology gaps, behavior that leads to inappropriate drug use, weak health systems, poor drug quality and counterfeiting, and excessive use of antibiotics in agriculture.
- New drugs, improved and scaled-up diagnostic and susceptibility testing, increased adoption of preventive technologies, and resistance-specific research are needed to slow the spread of drug resistance.
- Making sure a patient gets the right amount of the right drug and knows how to take it correctly is a responsibility that extends across the pharmaceutical supply chain—from manufacturer to patient.
- Resistance thrives when a country has insufficient or poorly trained health professionals, weak health system infrastructure, and poor regulation and enforcement.
- Increased use of antibiotics in agriculture can foster the development of resistant bacteria, which are transferred to humans through food consumption and human-animal contact.

All of the drivers must be considered in developing a comprehensive response to global drug resistance

Khalifa's Story *(continued from chapter 2)*
The malaria pills didn't work. Khalifa still felt terrible. High fever, awful diarrhea, and stomach pains. She went to the hospital and asked her colleagues at the laboratory to find out what was making her ill. As it turns out, Khalifa did not have malaria, but instead typhoid, a bacterial infection common to places like Gomoa, where sanitation is poor. The doctor gave Khalifa an antibiotic, ciprofloxacin, which provided a little relief, but also upset her stomach. Despite the side effects, she diligently completed the course of ciprofloxacin and felt somewhat better. But not for long. . . . *(continued in chapter 4)*

A first step in developing an effective global response to drug resistance is to understand its major drivers. These include a vexing mix of technology gaps, behavior that leads to inappropriate drug use, weak health systems, poor drug quality and counterfeiting, and excessive use of antibiotics in agriculture. 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 increased movement of people across borders guarantees that resistant microbes will move with them. All of the drivers must be considered in developing a comprehensive response to global drug resistance.

This report highlights **technology gaps**, **inappropriate behavior**, and **weak health systems** as key drivers of drug resistance, both locally and globally. However, superseding all of those is the **global leadership** gap. Before describing the drivers in each of the three categories, it is worth examining what remains missing in the leadership of global health that prevents a coherent response to drug resistance.

- Global health institutions do not prioritize drug resistance in their objectives, and therefore fail to provide adequate financial and technical support to developing countries. This is not just true for WHO—which clearly has the most critical leadership role to play—but also UNICEF; UNAIDS; the United Nations Population Fund (UNFPA); the World Bank; the Global Fund to Fight AIDS, Tuberculosis and Malaria; and UNITAID, as well as major bilateral donors and foundations working in health. Through setting guidelines, procuring drugs and other commodities, investing in health system capacity, and influencing decisions of national governments, these agencies are all in a position to influence the future course of drug-resistant forms of disease.
- The global health legal framework does not clearly state countries' responsibilities regarding drug resistance. Specifically, the International Health Regulations (IHRs) indicate that cases of "new or emerging antibiotic resistance" are likely to be notifiable, as underscored by expert consultations on the IHRs.[1] Close coordination with developing country governments about how to respond to resistance conditions in their countries can help "break the silence" that contributes to lack of awareness. However, countries and even WHO itself do not have clear rules to follow for applying the IHRs for drug resistance. Clarification, guidance, and technical support will be needed for IHR signatories to take this on board, and without strengthened laboratory and surveillance capacity—as recommended in this report—they will be unable to respond.
- Terms, standards, and protocols to facilitate surveillance and reporting are unclear. For example, the International Classification of Diseases lists drug-resistant forms of several different diseases, but it appears that most countries are not collecting and reporting data using these classifications. Partly as a result, there are multiple and conflicting definitions of resistance mechanisms and pathogens. This hinders good surveillance and reporting.

To effectively address the major drivers of resistance—and they must be addressed—we need strong leadership from global health institutions, drug manufacturers, governments, health care providers, donors, and philanthropic organizations.

Missing and inadequate technology drives resistance

Drug resistance is a naturally occurring evolutionary phenomenon. The tools we employ to prevent, diagnose, and treat disease must therefore keep evolving too. Yet generating the technological developments needed to fight infectious disease is far from easy.

Drugs

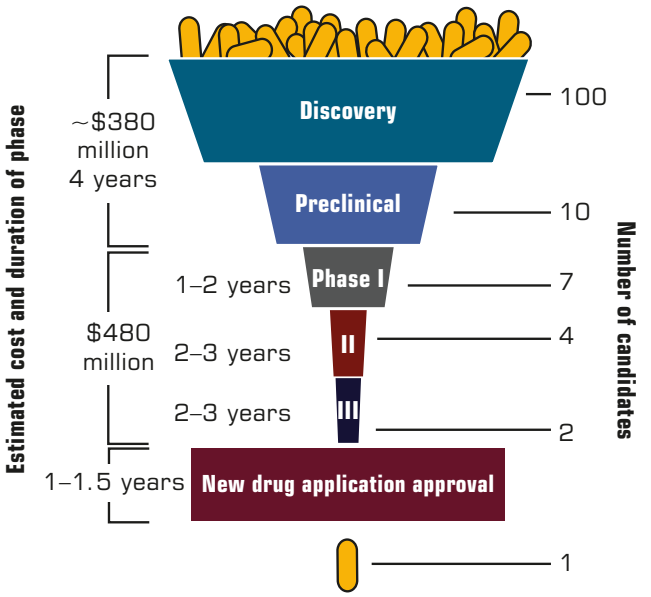
Infectious disease research and development—particularly for drugs and vaccines—was highly productive during much of the 20th century. However, new drug approvals have now declined, and many large pharmaceutical companies reduced or sold their

anti-infective portfolios. Basic science research on infectious diseases is under-resourced, which reduces even further the probability of developing truly new anti-infectives. Figure 3.1 illustrates the minuscule chances of successfully bringing a new candidate through the entire commercial drug development pipeline, though chances may be improved where pipeline decisions are less influenced by commercial concerns (for example, in a public-private product development partnership [PDP]). For some diseases, pipelines have remained so thin that old treatments are all we have. For example, there has been no new first-line TB drug for around 50 years, and this has given the microbe ample time to evolve resistant strains. Appendix B vividly illustrates these challenges.

Depressingly, where new drugs have been developed, resistance to them has often followed within several years, or even months. As chloroquine-resistant malaria became widespread, patients turned to SP, but this proved to be an extraordinarily vulnerable drug, and resistance emerged rapidly. Several reasons have been cited for this, including the lengthy amount of time the drug remains in the bloodstream (in other words, its long half-life), the previous use of pyrimethamine as a monotherapy, and the widespread use of sulfa drugs to treat bacterial infections.[2] Dosing levels in children may also have been suboptimal.[3] All these factors ensured that the malaria parasite was given lots of exposure to the active ingredients in SP and plenty of time to adapt.

The way drugs are formulated has a huge effect on the ability of microbes to develop resistance. We now know to avoid the use of monotherapies for diseases like TB, malaria, and HIV, and perhaps others, and instead to combine drugs that act on microbes simultaneously in different ways. Sadly though, monotherapies are still found on the market and, as noted previously, the use of artemisinin monotherapy appears to be helping the malaria parasite develop tolerance to artemisinin in Southeast Asia. Fixed-dose combination therapies—where different drugs are combined in a single pill—are the most reliable, provided the half-lives of the drugs can be aligned, as a patient is guaranteed to get an efficacious dose of all drugs. In addition, the patient is not tempted to take just one pill or to share pills with others, as can more easily happen if drugs are simply packaged together (for example, in blister packs). However, fixed-dose combination drugs are more challenging to develop and therefore more costly.

Figure 3.1
Probabilities of success in the drug development pipeline



Note: II and III refer to Phase II and Phase III stages of product development.

Source: Adams and Brantner (2006); DiMasi, Hansen, and Grabowski (2003); Lowell and Earl (2009).

The development of new drugs that are less vulnerable to misuse and to the emergence of resistance is a high priority. In the meantime, drug manufacturers can go a long way to help the situation by ceasing the marketing of monotherapies that are no longer recommended for use (that is, where combination therapy is recommended), and by packaging their products in ways that enhance adherence and give the patient and their healthcare provider the information they need to use drugs appropriately, within reasonable cost. Governments are also responsible for enforcing legal and regulatory standards to keep the drug supply safe and efficacious.

Diagnostics and drug susceptibility tests

Other technologies than drugs are needed if we are to delay drug resistance effectively. The lack of cheap, accessible, and reliable diagnostics, or failure to use those that are available, means diagnosis and prescribing are more often than not determined by a

patient's symptoms. The use of symptomatic diagnosis is most problematic for malaria and some bacterial infections since the symptoms can be so similar. This can lead to misdiagnosis and the use of inappropriate medicines.

Many countries have only limited (if any) technologies to perform drug susceptibility testing (DST) and some needed technologies have not yet been developed. For instance, a high priority for development is a molecular tool for detecting artemisinin resistance. Without these technologies, prescribers cannot know whether a patient's infection is likely to respond to the drug selected. Treatment generally proceeds on the assumption that patients do not have a resistant form of infection—but if they do, the condition then has ample time to worsen. Patients may then infect others and may not even return to receive different appropriate drugs.

Preventive technologies

Ultimately, the best way to reduce drug use, and thereby help limit the emergence and spread of resistance, is to prevent disease transmission. Effective vaccines for some key infectious diseases do not yet exist, for example, against malaria, HIV, and *Shigella* pathogens. An effective replacement vaccine for TB is needed. Other preventive technologies exist—bednets and condoms, for example—but are used improperly or inconsistently. Public health behaviors and environmental health are also important—drinking water and sanitation, hygiene and hand washing, and infection control strategies in clinical settings—but new technologies would no doubt help here too.

Resistance-fighting technologies

What kinds of specific innovation do we need to bolster our fight against drug resistance? Clearly, new classes of therapeutics will be needed, particularly antibiotics. Especially appropriate for the major public research agencies, such as National Institutes of Health in the United States and the European Union's research directorate, is the need for investment in basic systems biology on drug response and resistance that can uncover new targets for drug development, such as enhancement of host response. Improved dosage forms, shortened treatment courses, fixed-dose combination therapies, and user-friendly methods of drug administration will all help. Point-of-care diagnostics—particularly diagnostics that can screen for different infections simultaneously—and drug susceptibility tests would help ensure that patients get drugs that will work the first time around. Other innovations might help protect drugs directly, for example, by stopping microbes from destroying drugs[i] or excreting them before they can take effect,[ii] or might involve other ways to treat infectious disease without using drugs at all.[iii]

Behavior drives resistance

When people take too little, incorrectly prescribed, counterfeit, or poor-quality medicine, the possibility of resistance increases. Making sure a patient gets the right amount of a high-quality drug and knows how to take it correctly is a responsibility that extends across the pharmaceutical supply chain—from manufacturer to consumer. Drug manufacturers share responsibility with regulatory authorities to provide safe, quality-assured medicines and to monitor their continued effectiveness. Drug prescribers and dispensers also play vital roles in ensuring that medicines are selected and used properly, as patients turn to them for diagnosis, advice, and treatment. Patients must be informed about the health and economic costs of taking the wrong drugs or taking drugs the wrong way.

The current reality, however, is that collective responsibility is being hijacked by perverse incentives throughout the supply chain. As figure 3.2 shows, and the rest of this section describes, each group has different incentives driving its actions, and too often these incentives are misaligned and lead to inappropriate drug prescribing, dispensing, and use.

Drug manufacturer behavior[iv]

Although at the "upstream" end of the supply chain, great attention is paid to achieving quality in the manufacturing process,

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i. For example, the chemical structure of some antibiotics can be altered to overcome the effects of 'drug modifying enzymes' produced by resistant bacteria.

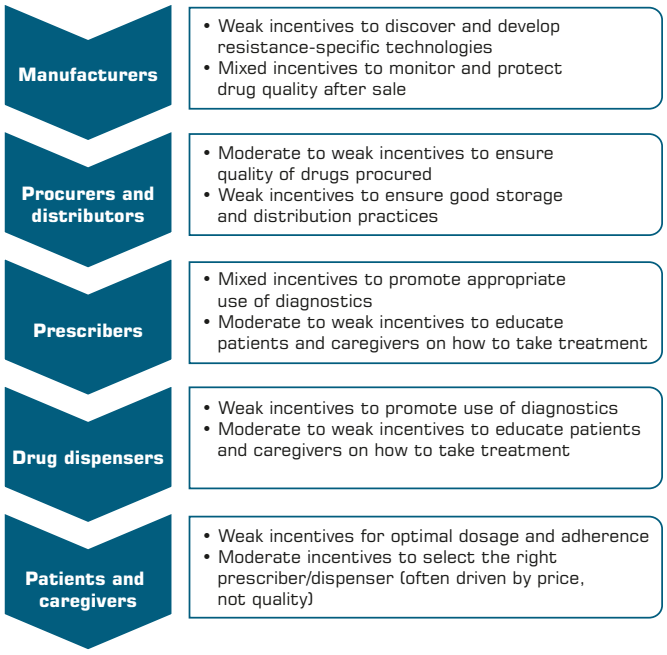
ii. A good explanation of efflux pump inhibitors can be found at http://www.mpexpharma.com/efflux.html.

iii. For example, treatment of diarrheal disease with improved electrolytes or probiotics (both areas of research that recently benefited from funding by the Bill & Melinda Gates Foundation); or destruction of the malaria parasite using nondrug technologies (see http://www.ibridgenetwork.org/columbia/ir_m09-014 for one relevant line of research).

iv. This discussion applies to nondrug technology, such as diagnostics, in many respects.

In many countries, appropriate dispensing of medicines is no greater among licensed professionals than among informal drug sellers

Figure 3.2
Misaligned incentives exist throughout the drug supply chain



some manufacturers[v] do little to monitor drug quality and use after sale and have little incentive do to so.[4] Perversely, drug companies have an interest in maintaining the quality of their products and face risks if their drugs become compromised as they move through distribution channels, but they have little reason to publicize resistance occurrence, or even monitor it.[5] They also have limited direct control over distribution and dispensing of drugs, and seek primarily to maximize sales.

As a result, pharmaceutical industry involvement in protecting drugs from improper distribution, storage, dispensing, and use is minimal and depends on individual company practice. A large percentage of developing countries lack the procedures for monitoring drug quality that are common in developed countries. A 1999 WHO survey revealed that only 40 percent of low-income and 46 percent of middle-income countries required sampling and testing of medicines at the procurement or distribution stages—and fewer countries actually carried out such checks. Post-marketing monitoring of drug quality is a gap that is not addressed by either producers or regulators.

The potential for the misuse of drugs that can lead to resistance extends to the way drugs are packaged, including the contents of package inserts. In the many countries where drugs are sold without prescription, the only information a consumer receives about the drug they purchase may come from the packaging or inserts—although they are not always available with the product. Because they are largely oriented to meeting drug safety concerns, package inserts rarely mention the connection of inappropriate drug use to drug resistance. The language is highly specialized and difficult for patients and (sometimes) providers to understand. Sometimes the inserts are not written in the local language.

More broadly, the financial rewards to manufacturers do not always coincide with health goals such as controlling resistance. Drug makers aggressively market their merchandise by offering financial bonuses and other incentives to prescribers and dispensers to increase sales—often with unintended consequences. In the worst cases, manufacturers may provide misleading information to prescribers and dispensers. For example, a pharmaceutical company in India distributed leaflets recommending the use of rifabutin for MDR-TB, which is not effective and is contrary to the recommendations of the Indian public TB authorities and international guidelines.[6] To align incentives better, some have called for paying drug companies to reduce misuse of drugs.[7]

Prescriber and dispenser behavior

On the "downstream" side of the supply chain, it is critical to know where people in developing countries get their drugs and how much they know about the products they are getting. Developing country patients access drugs from formal and informal providers—from doctors, nurses, midwives, pharmacists, shop owners, and street sellers. Formal or informal, all of these providers have the collective responsibility to ensure that patients receive a full course of the right drug, along with correct information about how to take it.

v. In the following discussion of pharmaceutical manufacturers, this report refers only to good manufacturing practice–compliant innovator and generic manufacturers. The report does not specifically address resistance issues caused by counterfeit products.

Standard treatment guidelines do not exist in a majority of developing countries

However, the reality is that even formal, public sector health professionals receive little, if any, systematic training in drug resistance. Shockingly, in most countries surveyed by WHO, appropriate dispensing of medicines is no greater among licensed professionals than among informal drug sellers.[8] Experienced developing country prescribers rarely have opportunities to update their knowledge about new treatment options, except with often limited information from drug regulatory authorities, which comes infrequently, if at all.

Perverse incentives for health-care professionals have become a normal part of health-care practice in both rich and poor countries. Providers commonly feel (real or perceived) pressure from their patients to treat with drugs. Under such circumstances, the provider's incentive is to satisfy the customer and prescribe a drug, whether it's necessary or not. Appeasing the patient may lead to a better relationship and better chance that he will be a repeat customer. Another factor that drives behavior during the patient-provider interaction is a patient's expressed desire for a specific drug, often as a result of industry advertising. Once again, to please the patient the provider may offer an inappropriate drug.

Where prescribers are also drug dispensers, incentives can become terribly perverse. Providers who make a profit from drug sales or from the consultation that accompanies a drug handout have the incentive to make a "transaction." Historically, providers in China, for example, received a good part of their income from drug sales, rather than from services charges.[9] The Chinese Ministry of Health began to address this problem in 2004 by placing price limits on hundreds of prescription drugs. And, in December 2009, China included guidance for physicians on the use of antibiotics for the first time in the national Medication Catalogue and prohibited payments from pharmaceutical manufacturers to doctors.[10] While the official actions are laudable, implementation among practitioners is lagging, according to recent media reports.[11]

Patient behavior

Patient drug choices are affected by a number of factors, including stigma, cultural preferences and beliefs, gender norms, and the cost of accessing medicines. Stigma can be a direct barrier to drug adherence.[12] When stigma prevents patients from disclosing their HIV status, it becomes difficult for them to take pills in public.[13] Other reasons patients do not follow proper treatment include adverse side-effects of drugs, complex treatment protocols, or simply feeling better after taking a partial treatment. In many parts of the world, cultural preferences and beliefs, such as in the higher effectiveness of multicolored capsules over plain ones or injectables over pills, affect individual drug-taking behavior.[14] All contribute to behaviors that favor resistance development.

Programmatic challenges that interrupt treatment—such as supply inconsistencies and patient care and transport costs—also play a critical role in driving resistance.[15] Where services are costly or far away, patients will often select the drugs themselves and purchase them from an unlicensed dispenser. Self-medication can lead to use of the wrong drug or less than the required full course of a drug.

Informal dispensers, who sell drugs without a prescription, are estimated to be the most common source of drug access for a large percentage of the world's population. A recent review of malaria treatment in sub-Saharan Africa, for example, found that 15 to 83 percent (median approximately 50 percent) of caregivers sought treatment and advice for childhood illness in a private, informal sector shop.[16] In those outlets, medicine is often sold a few pills at a time, as this is more affordable than purchasing a complete regimen.

In summary, the incentives motivating the behavior of actors along the supply chain—from drug manufacturers to those who procure and distribute medicines, from prescribers and dispensers to those who ultimately consume the drug—are frequently not aligned, leading to behavior that drives resistance. It is widely believed across the entire range of public health and clinical treatment programs that behavior change is the most difficult outcome to achieve.

Weak health systems drive resistance

Resistance thrives in the presence of insufficient or poorly trained health professionals, weak or nonexistent infrastructure, and poor regulation or enforcement. Each has a distinct role in preventing and detecting drug resistance, but none can work in isolation. The current attention being paid in the global health community to health system strengthening must begin to take account of the contribution weak health systems make to drug resistance and, hence, to poor treatment outcomes.

Laboratories are the Achilles' heel of global health

Scarce human resources

Where adequately trained health workers are in short supply, it is extremely difficult to ensure that drugs are prescribed, dispensed, and used appropriately. Global partnerships and other donor-financed initiatives tend to focus on increasing developing countries' ability to train and retain doctors, nurses, and midwives.[17] While these professionals have a significant impact on patient outcomes, less attention has been given to the two other professional groups vital to protecting drug efficacy: laboratory workers and pharmacists.[vi] Laboratory-based testing, quality prescribing, and patient monitoring are indispensable to understanding and preventing drug 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 had 213. Bangladesh identified 1,985 such workers in 2005.[18] Even where there are laboratory workers, they often lack necessary training and equipment, and where capacity for testing and analysis is weak, clinicians can be reluctant to use laboratory diagnoses.[19]

Inadequate laboratories

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.[20] Even though simple microbiological techniques exist to determine drug susceptibility for most bacteria, many countries have—at best—one or two laboratories with such capacity. If and when a local clinic sends a sample for testing, usually to a national reference laboratory if one exists, it can take at least a month and in some cases several months for a result to come back—if it comes back at all—because of overload or a lack of efficiency at the testing laboratory and transportation time. Such delays put the well-being of the patient—and others around them—at risk.[21] Finally, lack of a standard protocol for measuring resistance impairs data-sharing and comparison across laboratories and therefore prevents good public health surveillance of resistance and improvements in clinical practice guidelines.

Poor surveillance

Trends in drug use and resistance are not routinely monitored in most developing countries, in part because of weak laboratory infrastructure and related recordkeeping. Unlike the transmission of diseases such as avian influenza or severe acute respiratory syndrome (SARS), no early-warning system exists to alert public health agencies and health providers to watch for resistance signs. Patients rarely know why an illness has worsened or become untreatable, and prescribers may choose ineffective medicines because they are unaware of local resistance patterns. Health systems often do not record treatment failure, even when it results in death.

Insufficient regulation

Regulation—from the point of drug development and manufacture to when a drug is dispensed to a patient—is fundamental to ensuring that drugs will work if used appropriately. National drug regulatory agencies (NDRAs) are vital in this process, but many developing countries struggle to protect their populations from unsafe and poor-quality drugs because of limited resources and the challenge of monitoring drug flows within and from outside their borders. Enforcement is often weak—either because appropriate laws are not in place or enforcement capacity is low, or both. Regulators focus on enforcing quality manufacturing standards, while neglecting to detect substandard products beyond the factory gate. As a consequence, regulators may have little knowledge about the quality of drugs circulating in their countries and where they originated. Further, standard treatment guidelines do not exist in a majority of developing countries, and the proportion of prescriptions adhering to guidelines varies widely where the guidelines do exist.[22]

While the weaknesses of a single national agency create health and safety risks for people in its particular country, poor regulatory capacity becomes an even larger problem when viewed in a regional context. A country's policies and actions—or inactions—to regulate its drug supply have implications for other countries, even those well beyond its immediate borders, because of disease transmission and international trade in medicine.

vi. Defined by WHO for the Global Atlas of the Health Workforce as including "laboratory scientists, laboratory assistants, laboratory technicians, radiographers and related occupations." An interesting exception to this rule includes 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." (McCoy, McPake, and Mwapasa [2008].)

Some 41–47 percent of malaria drugs sampled in Africa and India failed to meet quality standards

The deficiencies that impair good regulatory performance are both technical and organizational. On the technical side, NDRAs have uneven knowledge about the scale of drug resistance from country to country, lack common indicators of the problem, and have varying regulatory authority and capacity. On the organizational side, the task is complex—requiring a combination of scientific, legal, industrial, and law enforcement expertise—and is frequently spread among multiple agencies. Enforcement gaps are likely to grow when differing resources and effort cause neighboring countries to take vastly different approaches to monitoring drug distribution and usage.

Drug quality is also a critical concern and shared responsibility of drug regulators. To be effective and prevent resistance, drugs must contain the appropriate amount of active ingredients. Substandard drugs,[vii] which can be found in the public and private sectors alike, do not meet this criterion because of poor-quality manufacturing, packaging, transportation, or storage conditions, or as the result of outright counterfeiting. WHO estimates 30 percent of drugs sold in Africa are substandard, and a recent study in five African countries and India found that 41 to 47 percent of drugs sampled did not meet all quality standards.[23] Regulators in developing countries exert varying degrees of oversight or control over postmarketing aspects of the drug supply—with greater attention to drug safety than to quality.

The result in many resource-limited settings is a largely unregulated pharmaceutical market—a drug bazaar—where substandard and counterfeit products circulate freely in both the private and public sectors and patient reactions to drugs are rarely documented. This environment drives the emergence and spread of drug resistance.

Nonhuman drug use drives resistance

A final, yet very important, driver of drug resistance in humans is our collective approach in industry and policy-making towards animal health and food production. Veterinary drug use is relevant, but of greatest concern is the use of antibiotics in agriculture. Sub-therapeutic use in food animals (deriving from the financial incentives of being able to promote rapid growth and earlier marketing, and to reduce the incidence of disease and cut costs) is particularly controversial. It fosters the development of resistant bacteria in animals, which can then transfer to humans through meat and other animal products or through direct human-animal contact.

There is also evidence of widespread and increasing use of antibiotics in aquaculture—including as prophylaxis—in both developed and developing countries.[24] And antibiotics are used to stave off infections in food crops,[25] which can absorb antibiotics from soil, manure, and water.[26] Antibiotic residue in foods may accelerate the development of resistant bacteria in humans and is therefore cause for concern. The health risks to humans are still hotly disputed, but the volume of antibiotic use in agriculture is staggering, and greater attention to appropriate levels and reasons for use is needed.

Recent evidence from Canada, the United States, and Europe suggests the problem of antibiotic overuse and emergence of resistance in animals is even more severe than previously acknowledged. 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) suggests that more than 20 percent of human MRSA infections in the Netherlands derive from an animal strain.[27]

Less is known about the extent of antibiotic use in livestock across Africa, Asia, and Latin America. However, as developing economies become increasingly industrialized it is likely that antibiotic use will increase in largely unregulated environments. The lack of data on drugs in agricultural use in developing countries prevented the Working Group from analyzing the evidence and developing policy solutions to this driver of drug resistance. We recommend additional research in appendix A.

vii. According to WHO, "Substandard medicines (also called "out of specification products") are genuine medicines produced by manufacturers authorized by the NMRA [National Medicines Regulatory Authority] which do not meet quality specifications set for them by national standards. Normally, each medicine that a manufacturer produces has to comply with quality standards and specifications. These are reviewed and assessed by the national medicines regulatory authority before the product is authorized for marketing."

Notes

1. WHO (2008d).
2. Gatton, Martin, and. Cheng (2004).
3. Barnes et al. (2006).
4. WHO (2009b).

At least 70 percent of all antibiotics consumed in the United States are fed to animals

5. Outterson (2009).
6. Macleod promotional flier.
7. Kessleheim and Outterson (2010).
8. WHO (2004b).
9. Harbarth and Oberlander (2004).
10. *Global Post* (2009).
11. *Telegraph* (2010).
12. Kumarasamy et al. (2005).
13. Kumarasamy et al. (2005).
14. Nordberg, Stålsby Lundborg, and Göran (2004).
15. Bennett (2010).
16. Goodman et al. (2007).
17. http://www.who.int/mediacentre/news/releases/2006/pr26/en/index.html and http://www.lancet.com/journals/lancet/article/PIIS0140-6736(10)60450-3/fulltext.
18. Global Atlas of the Health Workforce. http://www.who.int/globalatlas. Accessed September 17, 2009.
19. Polage et al. (2006).
20. Berkelman et al. (2006).
21. Shin et al. (2008).
22. WHO (2004), p. 89.
23. Bate et al. (2009).
24. Cabello (2006).
25. McManus et al. (2002).
26. Kumar et al. (2005).
27. Pollan (2007).

4
The current response

Chapter at a glance

- Limited data on drug resistance trends hide the evidence required to make resistance a high priority for donors and governments.
- Considerable financial, managerial, and political support is needed to broaden and scale up existing disease- or country-specific initiatives that have shown promise in improving prescribing and dispensing behavior.
- Regional cooperation can help drug regulators enforce drug quality and anticounterfeiting laws.
- A recent proliferation of product development partnerships and other new forms of collaboration offer a promising platform for cooperation on resistant-specific technologies.

Khalifa's Story *(continued from chapter 3)*

A few months after finishing her first course of ciprofloxacin, Khalifa started experiencing the same symptoms as before. She went back to the hospital—the lab results were even worse and she was prescribed ciprofloxacin again. In fact, since she began feeling sick, she has taken ciprofloxacin five times. Yet, she is not getting better.

When Khalifa took her new ciprofloxacin prescription to the pharmacy, the pharmacist remembered her previous visits and suggested she try another antibiotic instead—azithromycin. This prescription was much more expensive than ciprofloxacin—US$11 a course instead of US$3 for ciprofloxacin—but Khalifa purchased it and was careful to take every dose as the pharmacist advised. She completed the medicine and went back to the hospital. She could not believe it—her lab results showed she was not cured.

Khalifa's typhoid infection may be resistant to both ciprofloxacin and azithromycin. But there is no easy way to know this—the closest labs that can determine what drugs her infection will respond to are in Accra, which is hours away by car. Without this information, how can Khalifa's doctor choose a treatment that works?

Assuming the resistance profile is confirmed and the strain she has is resistant to both ciprofloxacin and azithromycin, what are the alternatives? Ceftriaxone, an injectible, may work. But at US$49 a course from the hospital dispensary in Ghana, the drug is not affordable unless a patient has medical insurance coverage. *(continued in chapter 5)*

The previous chapter highlighted lack of leadership, a technology gap, inappropriate behavior, and health system weaknesses as important drivers of drug resistance, both locally and globally. Before setting out recommendations to meet the challenge of resistance worldwide, as we do in chapter 5, it is worth examining the current efforts in each of these categories of drivers, and where they fall short. We begin with leadership.

Shortfalls in leadership on drug resistance

Drug resistance is widely recognized as a serious threat by the global scientific community. The risks it poses are far less understood by high-level policymakers. The drug resistance response tends to fall into the interstitial spaces between public health policy and private decision-making. Past efforts to energize global action to more comprehensively address drug resistance have been sidetracked by poor timing or over-stretched budgets. A few examples are representative of the lack of sustained high-level attention. In an unfortunate coincidence of timing, a WHO Strategy on Antimicrobial Resistance was launched on September 11, 2001. As a result, the action plan prepared for the Strategy did not get carried out, and over time the interest in cross-cutting drug resistance at WHO withered, even while disease-specific attention grew. For many years, the U.S. Government provided support for research, technical support, surveillance, and policy development on drug resistance in developing countries through an annual budget appropriation to the U.S. Agency for International Development (USAID). That support has become narrowed to programming in only a few areas.

In spite of World Health Assembly resolutions, Institute of Medicine reports, and dedicated advocacy, the attention to global drug resistance has become increasingly disease- and program-specific since the mid-2000s. While these programs offer important lessons—especially from the strong gains made to improve the information base on TB and malaria resistance—they do not offer reassurance that attention from donors and technical agencies to drug resistance is going to be sustained or comprehensive.

The existing information base

The combined efforts of existing small-scale and disease-specific programs and networks offer a woefully piecemeal picture of drug resistance globally. The lack of systematic data on drug resistance trends at a country or even regional level leads to a circle of neglect: Insufficient awareness makes drug resistance a low priority for donors and governments, while a lack of attention and resources keeps hidden the evidence required to address drug resistance in a focused manner. Appendix F provides a compendium of current drug resistance information sources.

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.[1] The

international donor and technical communities as well are siloed by disease and population, and few opportunities arise to appreciate the ways in which action across diseases would improve protection for all drug classes. For instance, vertically-oriented disease programs established by donors generally maintain their own laboratory and surveillance systems. While each disease, and even each strain of pathogen, has specific resistance characteristics, with specific treatment to meet patient needs, the primary drivers of resistance have much in common—and only by aggressively and immediately beginning to identify and neutralize those drivers across, not just within, the current vertical silos is there hope for a successful outcome.

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

- **Scientific data** (for example, molecular information) to aid understanding of how pathogens are evolving to resist different drugs.
- **Population data** (for example, epidemiological data) such as that generated through routine surveys and public health surveillance systems, to aid understanding of where and to what extent drug resistance is emerging and spreading.
- **System data** (for example, drug prescribing, dispensing quality, and use information and cost data) to aid understanding of the reasons why drug resistance is emerging and spreading.

Scientific data

A number of disease-specific global databases hold scientific data related to drug resistance. Examples include the Stanford University HIV Drug Resistance Database, the International TB Genotype Database, WHO TB Specimen and Strain Banks, and very recently the WorldWide Anti-Malarial Resistance Network. Such databases are generally managed by small expert teams and are often housed in academic or research institutions. Very few are sustainably financed, and several databases have folded in recent years for lack of funds.[i] There is a need to build on existing knowledge and networks with specialized expertise, such as the network of more than 60 country-level chapters maintained by the APUA.

Population data

Data charting the spread of drug resistant forms of disease are, not surprisingly, much more likely to be collected and analyzed in high-income countries than in resource-constrained settings. Both the United States and Europe 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. Regional examples include the Asian Network for Surveillance of Resistant Pathogens and the Latin American Antimicrobial Resistance Monitoring/Surveillance Network (described in box 4.1). However, even in low-income countries, drug resistance surveillance can be made routine with sufficient funding and other support, as demonstrated by the drug resistance–related research conducted at the International Centre for Diarrhoeal Disease Research in Bangladesh.[ii] A demographic surveillance site in East Africa was also effective for a period of time in collecting malaria drug-resistance data, but the effort was not sustained.

In low-income countries, weaknesses in laboratory capacity mean that DST is rarely carried out. Some technical assistance is now available to help laboratories undertake DST using basic microbiological techniques and to record the results in ways that aid both effective patient care and monitoring of trends. The WHO Collaborating Center for Surveillance of Antimicrobial Resistance has been doing this for more than two decades and has developed a simple software called WHONET for laboratories to download and deploy;[iii] however, the oversight and capacity building the center's team can offer is limited by its own severe resource constraints.

The substantial donor support for developing country laboratories has often come through disease-specific programs. Fortunately, broader laboratory strengthening initiatives have been launched in recent years, including the Global Laboratory Initiative (initiated by the Stop TB Partnership but increasingly able to support other disease-resistance testing), the WHO Regional Office for Africa laboratory accreditation scheme supported by a range of U.S. technical

i. Examples include the ARInfoBank, developed by WHO to capture data on antimicrobial resistance across diseases, and the Los Alamos HIV Drug Resistance Database.

ii. See http://www.icddrb.org/page_view.cfm?ID=26 and http://www.icddrb.org/page_view.cfm?ID=27 for examples.

iii. See www.whonet.org or http://www.who.int/drugresistance/whonetsoftware/en/ for more information.

Box 4.1
Using drug-resistance surveillance data to inform patient care and drug policy: the case of Latin America

In 1996, the Pan American Health Organization (PAHO/WHO) launched a microbiology laboratory strengthening program to identify bacteria and test their susceptibility to antimicrobial drugs. Now, 20 countries are participating in what has become the Latin American Antimicrobial Resistance Monitoring/Surveillance Network.[1]

The Network comprises 521 sentinel sites in provincial, hospital, and private laboratories.[2] These sites regularly report raw and analyzed data to national reference laboratories, where they also send complex samples for identification and susceptibility testing when necessary. Findings inform both the treatment of individual patients and national drug policies. Additional features include standardization of microbiology techniques and regional quality assurance and training programs that provide support to all member laboratories.

Surveillance trend data for the region, generated by this routine activity, reveals widespread and increased prevalence of resistance for both community and nosocomial pathogens such as MRSA, *S. pneumoniae, Escherichia coli, Haemophilus influenzae, Acinetobacter* spp, *Shigella* spp, and *Pseudomonas aeruginosa.*

Data collected through the network have informed the following policy developments:

- Treatment guidelines (new or revised) in Guatemala, Paraguay, and the Dominican Republic;
- Restriction of antibiotic sales in Costa Rica, Uruguay, and Venezuela;
- Creation of infection prevention and control committees or units within the National Ministry of Health in the Dominican Republic and Paraguay;
- Public awareness campaigns about appropriate drug use in Ecuador, Peru, Bolivia, and Paraguay; and
- Development of clinical guidelines for the *Treatment of Infectious Diseases* (4th edition, 2009).

The network does face resource and capacity challenges. The same constraints have plagued WHO's Western Pacific Regional Office, which once had a viable drug-resistance surveillance program before regional resources shifted to focus on SARS and then avian influenza. However, the PAHO network has been in place for 14 years and continues to grow, with limited external financing (roughly US$300,000 a year), which suggests this is a model that is replicable in other regions.

1. Argentina, Bolivia, Brazil, Canada, Chile, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay, U.S., and Venezuela. Colombia is joining in 2010.

2. Patient populations presenting at these facilities may not accurately represent the drug resistance prevalence in the given population. There is, therefore, also a need for nationally representative surveillance data to assess the true extent of the problem.

agencies,[2] and new World Bank–supported programs in Africa.[iv] These and other initiatives are needed to increase DST capacity and to lead to better drug-resistance data collection and analysis.

Meanwhile, WHO collects the limited data available from low-income countries and maps changing patterns of drug resistance as best it can. In the absence of laboratory and surveillance capacity from different levels of the health system in all countries, these data tend to be drawn from field studies, supranational and sometimes national reference laboratories, and disease-specific global and regional networks. In some cases, most notably for TB, data are aggregated, published, and proactively disseminated. For

iv. Other relevant but modest initiatives include the American Society of Microbiology's LabCap program; training and mentoring facilitated by organizations such as the Mérieux Foundation and the Clinical and Laboratory Standards Institute; and the WorldWide Antimalarial Resistance Network.

Policymakers and practitioners often must base their decisions on patchy drug resistance data or, in many cases, on no data at all

malaria, a large database has been developed by WHO to record the results of country studies, with one major report issued in 2005.[3] However, many data are not put into the public domain, or are difficult to find or obtain. WHO reports themselves show significant gaps (for example, there are countries with no data). In 2005 APUA's Global Advisory on Antibiotic Resistance Data report compiled resistance data for all major infectious diseases from public and private surveillance systems.

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 monitors information streams for disease outbreak warning signs and then builds teams to undertake analysis and collaborative planning. Another relevant mechanism is ProMed, an informal global electronic reporting system for emerging infectious disease outbreaks that draws on information shared through email and electronic discussion boards. ProMed data are reflected on HealthMap—a map-based disease-alert platform.[v] Several of these tools already capture limited drug-resistance information. 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 (for example, from donors or foundations such as Google.org, which has invested in all the examples above), they could be used to fill a gap in our knowledge about drug resistance across diseases while more systematic local surveillance capacity is built. More traditional surveillance methods, such as demographic surveillance sites, can also be utilized to track resistance information.

System data

Tracking the use of specific drugs in different localities would be a useful step in identifying locales where a confluence of factors increases the emergence and spread of resistance. 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 are implementing 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 Health routinely collect information on drug sales in some Latin American, Asian, and African markets. New publicly supported global initiatives work to improve data collection and sharing, such as the Medicines Transparency Alliance, International Network for the Rational Use of Drugs, and WHO Medicines Use Database.[4] New technology hints at the potential to make detection and surveillance faster and cheaper in the foreseeable future. This is a rapidly evolving field and information resources are likely to be strengthened over the coming years.

It is not enough to just 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 (for example, global health donors and 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, the current understanding of how drug resistance is evolving and spreading across the developing world, and across the globe 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 (for example, in 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 data at all.

Regulatory capacity strengthening

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

v. See http://www.promedmail.org and http://www.healthmap.org for more information.

formalize the interdependence that exists among adjacent countries by enhancing the incentive for collective action and reducing the incentives for free-riding on others' efforts. Existing regional networks vary according to the needs and challenges of the member countries, and need to have institutions and rules that guide the relationships and accommodate regional conditions. 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 and most parts of Asia.

The capacity of drug regulators to monitor drug quality and use is weak in developing countries. Regional cooperation shows promise for carrying out a range of needed activities related to medicine supply and use. For example, the PAHO Resistance Surveillance Network described above has strengthened the national capacity of countries in the Americas to address antimicrobial resistance. The Association of Southeast Asian Nation's economic ministers have also cooperated on drug quality and safety regulation in the region, among other pharmaceutical issues.[vi] Regional pharmaceutical forums have been supported by USAID to translate new research about treatment protocols into information for regulators about how to improve standard treatment guidelines and essential drug lists.

A regional network will only be as strong as the commitment of each of its members to collective decisionmaking and follow-through. Box 4.2 describes one regional effort in West Africa to strengthen NDRA monitoring and enforcement abilities. A new Africa-focused effort on regulatory harmonization is under way with the support of multiple donors.[vii] This initiative could serve as a mechanism to provide both foundational training on regulatory roles and functions and specific training on drug quality and anti-counterfeiting monitoring and response.

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.[5] Nevertheless, the World Bank study points to 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.

Innovations to slow drug resistance

Product development partnerships

There has been a recent proliferation of PDPs focused on infectious diseases prevalent in developing countries. PDPs are donor-funded nonprofit organizations that bring together researchers from academia, government, and industry under a common management and funding framework. This enables different lines of research to be prioritized through a portfolio approach, increasing efficiency and productivity. Each PDP generally has its own focus, either on a particular disease or technology.[viii] The most visible of these investments to date have been for malaria and TB. Some of the PDPs—most obviously the Medicines for Malaria Venture—were established specifically in response to growing concerns about the lack of reliable treatment options resulting from resistance. However, while plans have been laid and pipelines have begun to be replenished to replace the old drugs for TB and malaria, this is not the case for anti-infectives.

While most PDPs are too young to claim marketed products, they can boast of populating once-negligible pipelines with exciting candidates, and a few can already claim real results. For example, the Drugs for Neglected Diseases Initiative partnered with Sanofi-Aventis and the Brazilian government to develop and launch two new fixed-dose ACTs for malaria; the Medicines for Malaria Venture has also brought a number of

vi. Sectoral Mutual Recognition Arrangement for Good Manufacturing Practices Inspection of Manufacturers of Medicinal Products.

vii. DFID, the Bill & Melinda Gates Foundation, and the Clinton Health Access Initiative are working with WHO to support a continental harmonization initiative in Africa; other donors and agencies are supporting regional efforts of the Southern African Development Community. However, these efforts do not yet focus on sharing information about drug quality or drug-resistance data. The Medicines Transparency Alliance does support the disclosure and dissemination of data on drug quality—albeit for just seven countries currently.

viii. Examples of PDPs focused on diseases of the developing world include PATH's Malaria Vaccine Initiative, Areas' TB vaccine initiative, the TB Alliance, the International AIDS Vaccine Initiative, and the International Partnership for Microbicides. The nonprofit pharmaceutical company, Institute for OneWorld Health, has a similar focus.

There currently are no Web-based platforms specifically focused on drug resistance

Box 4.2
The WADRAN: a regional network without sustained support

The West African Drug Regulatory Authority Network (WADRAN) was created under the institutional auspices of ECOWAS, the UN Regional Economic Community in West Africa, to develop common drug policies across countries in the region. Among its goals was to strengthen regulatory capacity against poor-quality and counterfeit drugs.

Leadership on the issue came from Dora Akunyili, former head of the Nigerian National Drug Regulatory Authority, who became a global phenomenon in her fight against drug counterfeiters. The WADRAN garnered support from the European Union to implement regulatory strengthening aimed at meeting International Organization for Standardization (ISO) standards for laboratory quality, improving pharmacy management, and providing training on appropriate medicine use. The group recognized that open borders implied that poor drugs in one country created a common threat to all the region's countries and identified regulatory capacity as the most important barrier to effective quality improvement.

The WADRAN was one in a series of attempts to harmonize African drug regulatory standards and practices. Despite recognizing the value of a common understanding and transparency across countries on regulatory efforts, WADRAN has been stymied for lack of sustained resources and leadership.

Source: Interview with Dr. Hashim Yusufu, director of technical services at the National Food, Drug Administration and Control Agency of Nigeria.

new antimalarials to market. There are multiple new TB drugs in clinical development with strong promise to shorten treatment duration. The Foundation for Innovative New Diagnostics partnered with WHO and CDC to conduct lot-test evaluations of dozens of marketed rapid malaria diagnostics to inform procurement agencies and health workers about their quality and reliability.

New forms of collaboration

In addition to the proliferation of PDPs, recent years have seen a shift toward increased collaboration in health research more broadly. This trend is promising for relatively neglected fields of research, including infectious disease, but 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, research scientists with expertise in drug discovery have dispersed either into hundreds of smaller pharmaceutical and biotech companies, or into academic, nonprofit, or government labs. To fill their pipelines, the big drug makers are increasingly in-licensing candidates from smaller entities. Other forms of collaboration have been supported with public funding. The Innovative Medicines Initiative of the European Commission is a public-private partnership to identify R&D bottlenecks. It would be well suited to support academic and industry researchers to explore jointly issues related to drug resistance.

In line with this trend, a number of Web-based collaborative research platforms have emerged, allowing innovators to share ideas, research outputs, and other information (see box 4.3 for examples). Some of these platforms are membership- or subscription-based, or otherwise operate behind closed doors. Some are geared toward the commercialization or on-licensing of patented innovations, while others are open-source collaborations.

The 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. This approach is likely to be particularly valuable in discrete, highly specialized fields of research, such as the development of technologies to interrupt the emergence or transmission of drug-resistant forms of disease. However, there currently are no Web-based platforms specifically focused on drug resistance.

More traditional sources of support for health research and development are giving new attention to drug resistance. The Bill & Melinda Gates Foundation, U.S. National Institutes of Health, and UK Wellcome Trust have all expanded grant making in the

Rarely do core curricula or continuing professional development education for health professionals systematically incorporate the development and prevention of drug resistance

Box 4.3
Examples of Web-based collaborative research platforms

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

- iBridge and the Massachusetts Technology Portal are examples of Web-based platforms, specific to groups of academic research institutions, which 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 is a subscription-based for-profit platform allowing researchers to store and selectively share data such as bioassays and chemical structures.[1] It has recently been opened to noncommercial uses.
- Open Source Drug Discovery is an open-source R&D platform focused on neglected diseases. It "aims to provide a platform for knowledge sharing and collaborative research leading to identification of novel drug targets" and is initially focused on TB.
- GlaxoSmithKline's "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 the company's patent filings and expertise in small molecule pharmaceuticals.[2]
- There have been several managed openings of pharmaceutical company compound libraries, usually for limited searching related to a specific disease (for example, Pfizer's arrangement with WHO/Tropical Disease Research to allow screening of compounds for parasitic diseases, and Merck and Eli Lilly's collaboration to amass compounds for TB-related screening by the Infectious Disease Research Institute).

1. CDD and InnoCentive October 1, 2008. Press release at www.collaborativedrug.com/blog/news/files/2008/10/cdd-innocentive-press-release.pdf; IFPMA website. Available at: http://www.ifpma.org/issues/index.php?id=247; Hutton (2008).

2. See http://www.gsk.com/research/patent-pool.htm for more detail.

field of drug resistance.[ix] Evidence from the Bill & Melinda 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 more than 1,200 applications in its two grant-making rounds, of which they were able to fund 35.[6] That leaves hundreds of researchers in need of funding to advance their ideas, discoveries, and innovations against drug resistance.

The current resistance-inducing behavioral landscape

Given prescribers' and dispensers' potential to influence patient drug use and change consumer practice, there is perhaps no greater opportunity for reducing drug resistance than by motivating these actors to engage in practices that promote appropriate use of medicines.[7] The following section highlights current —patchy—efforts to improve prescribing, dispensing, and, ultimately, drug use in developing countries. While academic papers have been published about efforts to improve drug provision and drug-resistance education and communication, the details of what has worked best, where, how, and why have not been disseminated widely to a broader global or national health audience—especially to other countries searching for effective solutions.

Education to improve prescribing and dispensing

Despite an abundance of developed country research showing that continuing professional development can result in changed professional practice and improved health outcomes,[8] efforts to encourage resistance-reducing prescribing and dispensing are minimal and inadequate. While some training programs on the

ix. At the Bill & Melinda Gates Foundation, this includes the Grand Challenges Explorations program, which funded basic science discovery related to resistance for two years. The Foundation provided substantial support to Medicines for Malaria Venture for later-stage development of alternatives to artemisinin for malaria treatment. At the U.S. National Institutes of Health, this comprises a broad portfolio of resistance-related basic science research, primarily on HIV/AIDS. The Wellcome Trust supports drug discovery and translational research related to malaria, hepatitis, MRSA, and other multi-drug-resistant bacteria.

A study in Mexico found that after consumer education, there was a 35 percent decrease in the amount of antibiotics consumed

rational use of medicines for health professionals do exist (such as those run by WHO's essential medicines and pharmaceutical policies department), rarely do core curricula or continuing professional development education for health professionals systematically incorporate the development and prevention of drug resistance (see box 4.4 for a counterexample).

Continuing education courses on rational drug use that do exist often are offered through international nonprofit groups such as APUA, the International Network for the Rational Use of Drugs, universities (such as the Drug Policy Research Group at Harvard University), and donor contractors that provide technical assistance (such as USAID-funded projects like Strengthening Pharmaceutical Systems, housed within Management Sciences for Health), in conjunction with national counterparts and often with support from and in collaboration with WHO. Most such courses are funded through vertical program funds and are often disease-specific. Specialty society materials, such as practice guidelines from professional organizations such as the Infectious Disease Society of America, are also freely available online. However, these are not always most relevant to developing country experience.

Despite a rapidly changing drug and resistance environment, experienced developing country prescribers rarely have opportunities to update their knowledge about new treatment options. Even in countries with standard treatment guidelines, these guidelines tend to be poorly implemented, are infrequently revised (every six to seven years), and are rarely used by private sector providers. Where strategies have successfully increased the use of guidelines with improvements in antimicrobial prescribing practice, guidelines were actively disseminated, there was strong local involvement, and prescribers were encouraged to give feedback.[9]

Box 4.4
Drug resistance in medical curriculum in Zambia

Experience from Zambia has shown that when the moment is right it can be relatively easy to incorporate drug-resistance material into standard health professional curricula. In recent years, the Zambian government (working with the USAID-supported Rational Pharmaceutical Management Plus program and subsequently its follow-on program—Strengthening Pharmaceutical Systems) built and expanded a local country-specific coalition to contain drug resistance. Reform of the Zambian medical curriculum happened to coincide with creation of this coalition. Stakeholders at the University of Zambia and other coalition members acted swiftly to include drug resistance in the reform. Examples such as this one suggest that effective pre-service training can bring sustainable behavior change by sensitizing future health-care practitioners early on regarding the current issues surrounding drug resistance and their crucial role in preserving the effectiveness of available drugs.

Source: Joshi, Pollock, and Garrison (2004); Joshi et al. (2006); Joshi (2007, 2008).

Task shifting to increase patient knowledge about appropriate drug use

The importance of the dispensers' role in counseling and advising patients is being increasingly recognized. Improving consumer knowledge about appropriate drug use can have dramatic results. A study in Mexico found that 62 percent of patients purchasing antibiotics without a prescription were following clinical advice. After consumer education, there was a 35 percent decrease in the amount of antibiotics consumed.[10] The International Pharmaceutical Federation and others have argued that, if relieved of retailing responsibilities, pharmacists could make better use of their training to support the appropriate use of medicines. AMFm includes task shifting within an accredited dispenser model to improve patient knowledge and appropriate medicines use.

There is growing international interest in boosting the role of pharmacy services to strengthen health systems.[11] While pharmacist remuneration models differ in how they reward professional services beyond dispensing (such as counseling on adherence), stronger incentives for dispenser promotion of appropriate drug use are being tried, primarily in developed countries. There is scope for them to be adapted to developing countries, especially where social health insurance is being implemented.[12] More

Box 4.5
Three countries' attempts to improve access to and use of high-quality medicines

In Ghana, a CAREshop® franchise for essential medicines was established in 2002 by the nonprofit organization Ghana Social Marketing Foundation (GSMF) and its for-profit subsidiary GSMF Enterprises Limited, through conversion of selected drug shops into franchised outlets. The aim of the CAREshop program was twofold: (i) to improve access to reasonably priced, quality-assured essential medicines and supplies and high-quality dispensing services in under-served areas and (ii) to implement a franchise system among participating chemical sellers' shops to establish uniform standards, train personnel, monitor adherence to franchise standards, and create business incentives for adherence to those standards. In this model, the franchiser determines the prices charged by franchisees and controls the quality of services and products, including drugs.

In Kenya, a franchise model was implemented in 2000, through which franchisee shops that sell essential drugs are operated by community health workers, and franchisee health clinics are operated by nurses. Both the essential drug shops and the health clinics are managed by the franchisor, the Healthstore Foundation®. Franchisees are reimbursed only when they deliver drugs and services according to certain standards. Standards include efforts to ensure that patients are properly diagnosed and drugs are of high quality (the franchisor procures high-quality medicines from approved sources on behalf of all franchisees). Community awareness-raising efforts include availability of take-home education materials for patients. A similar scheme was recently introduced in Rwanda.

In Tanzania, a program was launched in 2003 to accredit private drug dispensing outlets. The Tanzanian Food and Drugs Authority oversees the quality of services and products sold by the accredited outlets (called accredited drug dispensing outlets, or ADDOs). The goals are to create a new class of high-quality pharmaceutical service providers and increase population access to high-quality drugs in areas that were underserved. In order to receive ADDO accreditation by the Ministry of Health, drug sellers must agree to abide by set standards and follow certain regulations. They are then entitled to business management training, access to a regional pharmaceutical wholesaler that serves ADDOs exclusively, the ability to legally dispense a larger range of drugs than informal sellers, and access to microfinancing. ADDOs receive training in rational medicines use.

The process of establishing an ADDO includes collection of qualitative information about local community behaviors and preferences regarding access to medicines. ADDOs have led to increased community access to essential drug products, higher-quality dispensing services, and some improvements in appropriate drug use indicators. ADDO implementation has improved community awareness of the importance of drug quality and treatment compliance. Consumers associate ADDOs with quality-assured drugs and services.

Some lessons have been learned about implementing dispenser certification that warrant dissemination. A coalition of partners from the public and private sector is important to a successful program, with the public sector responsible for monitoring and enforcement. The specific arrangements of the business model are important, including the procurement arrangements, range of products to be carried by the certified dispensers and other limitations on services,

(continued)

Dispenser accreditation increases consumer awareness of drug resistance

Box 4.5 (continued)
Three countries' attempts to improve access to and use of high-quality medicines

and representation for the dispensers at the central partnership organization. It is important to incorporate these aspects within the existing regulatory operations, rather than establish a parallel but ultimately marginalized system.

Depending on the ambition of the scheme, costs of formalizing drug dispensing can be very high, especially at the outset. Initial start-up with appropriate assessment and adaptation involves a multiyear investment in program development, stakeholder outreach, and establishment of supply channels. Ongoing costs for the drug seller training, licensing, and monitoring program can also be substantial. In addition, there could be continuing costs of a central organization. International donors have supported dispenser quality improvement in a handful of African countries and continue to experiment and assess the potential of these arrangements. The success of the ADDO program in Tanzania has prompted the Bill & Melinda Gates Foundation to support the East African Drug Seller Initiative to scale up private sector medicine dispenser models.

Source: http://www.msh.org/seam/reports/seam_ghana_careshops.pdf; http://www.msh.org/seam/reports/SEAM_Final_Report_Summary-Tanzania_ADDOs.pdf; Center for Pharmaceutical Management (2008); Health Research for Action (2006); Alphonse (2008).

broadly, there is interest and expertise among a range of professional associations to take a stronger hand in educating their members about rational drug use, and creating certification to monitor compliance. This includes professional associations of nurses and doctors.

Engaging the informal sector to encourage appropriate drug dispensing

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 regulatory enforcement mechanisms, may be a more realistic behavior change approach and have higher impact. Introduction of effective certification programs creates opportunities for consumers to differentiate quality products as they begin to associate certified "brands" of drug distributors with higher-quality drugs and service. Evidence on the impact of these initiatives suggests that involving informal providers can, at least to some degree and under the right circumstances,[13] improve access to high-quality medicines and pharmaceutical services.

Box 4.5 describes three African examples of formalizing drug dispensers.

Coordinated interventions that include engaging communities to improve drug use

Even without the formal program described above, coordinated interventions can change individual or community consumer drug-using behavior.[14] Training is an example. Where dispenser training is one component in a larger strategy to improve drug use involving community outreach/education, it is likely to have higher and more sustained impact. Skill-based workshop training of shopkeepers in rural Kilifi, Kenya, led to a significant increase in the percentage of medicine sellers giving appropriate drug dosages, from 5 percent to 30 percent. Training was accompanied by provision of job aids, ongoing monitoring, and community behavior change efforts. Another example from Kenya (Bungoma district) began with peer education (wholesalers to retailers) but later added a neighbor-to-neighbor component, which sought to increase knowledge about malaria among caregivers and increase demand for antimalarials.

In summary, 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. These efforts have often been multifaceted, involving components such as regulatory enforcement, peer interaction, outreach, and incentives.[15] Box 4.6 describes a more radical

Drug seller training improves appropriate dosing six-fold

Box 4.6
The AMFm model

AMFm is an innovative financing mechanism designed to save lives while slowing the spread of artemisinin-resistant strains of the malaria parasite. The facility was invented by an expert panel hosted by the U.S.'s Institute of Medicine in 2004, accepted as an additional "line-of-business" by the Global Fund to Fight AIDS, Tuberculosis and Malaria in 2008, received US$235 million of initial donor funding in 2009, and opened its doors to applications from public and private sector drug purchasers in May 2010.

AMFm was created because of resistance-caused obsolescence of the malaria drug chloroquine and concern among public health experts that widespread use of artemisinin monotherapy may prematurely rob the world of its best current drug against malaria. AMFm offers a global subsidy to bring the price of the resistance-inhibiting combination formulation of artemisinin, called artemisinin combination therapy, or ACT, low enough to push monotherapy and counterfeit malaria drugs out of the market. The goal is to make ACT so cheap that informal sector retailers will buy it from wholesalers instead of buying monotherapy and counterfeits.

AMFm received its first round of applications as this report went to press. In the coming years, donors and others will watch closely to determine whether the AMFm model (i) will successfully save lives while slowing the development of resistance in the case of malaria; and (ii) could be applied more widely as a general solution to the problem of drug resistance.

Source: Talisuna et al. (2009).

approach to improve medicine prescribing and use by using price as a tool for slowing drug resistance. 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. Several efforts seem to have improved practice in informal settings—at least over the short term.[16] But small-scale, unsustainable projects are not good enough. There is a glaring history of donors starting projects and then moving on to other efforts, whether it is for genuinely better opportunities or simply loss of interest. Regardless of the reasons why donors curtail these projects, patients suffer and public health systems are weakened.

Notes

1. Mechoulan (2007).
2. Centers for Disease Control (2009).
3. WHO (2005).
4. For more information, see WHO (2009). Medicines use in primary care in developing and transitional countries: Fact Book summarizing results from studies reported between 1990 and 2006. http://www.who.int/medicines/publications/primary_care_8April09.pdf.
5. World Bank (2007).
6. Private conversations with Gates Foundation employees and the Bill & Melinda Gates Foundation website. Available at: http://www.grandchallenges.org/Explorations/Pages/Introduction.aspx.
7. 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).
8. Davis et al. (1999).
9. Nordberg, Stålsby Lundborg, and Göran (2004).
10. Gonzalez (2008).
11. Smith (2009).
12. Bernsten et al. (2009).
13. Rutta et al. (2009).

14. See summaries of evidence from the 2nd International Conference on Improving Use of Medicines (ICIUM) at http://www.icium.org/icium2004/.
15. See summaries of evidence from the 2nd International Conference on Improving Use of Medicines (ICIUM) at http://www.icium.org/icium2004/.
16. http://www.icium.org/icium2004/recommendations.asp. See "Policies and Programmes to Improve Use of Medicines: Recommendations from ICIUM 2004" file.

5
Four practical steps to fight drug resistance

Chapter at a glance

- It will take a coordinated and balanced approach, supported by strong global leadership, to tackle drug resistance worldwide.
- Surveillance must be improved by collecting and sharing information across networks of laboratories and making sure that data are available to multiple audiences, including pharmacists, policymakers, and donors.
- The public and private sectors must work together to secure the entire drug supply chain—from manufacturer polices to drug dispensing practices.
- National and international support is needed to enable national drug regulators to work together to improve the quality of drug supplies.
- A Web-based marketplace to share resistance-specific research would enhance innovation across diseases and foster collaboration, investment, and partnership.

Information resources central to managing drug resistance should be treated as "global public goods"

The Center for Global Development (CGD) Drug Resistance Working Group has identified four recommendations that, taken together, will go far to contain and reduce existing and emerging drug resistance globally. Each has merit individually, but their strength in attacking the problem lies in taking a unified multifaceted approach to identify, contain, and respond to resistance, with both public and private sector involvement.

How do we expect these recommendations to make a difference to the neglected problem of drug resistance? Our attention has focused on the market failures that allow drug resistance to develop and spread in a largely uncontrolled and undetected manner through many regions of the developing and developed world. Thus, the specific recommendations aim to correct information gaps and asymmetries, reduce negative spillovers, and manage the common resource of drug efficacy so that it lasts longer.

This has led to a narrow set of specific solutions that rely on monitoring, accountability, and improving information to reach better decisions, from one end of the medicines supply chain to the other. The recommendations target the areas of greatest vulnerability in the provision and use of drugs for infectious disease: resistance information, supply chain integrity, regulatory capacity, and the technology pipeline. Together they will work to stimulate better behavior among health-care providers, regulators, and consumers so that their decisions reflect society's true interest in maintaining effective and sustainable drug access to treat infectious diseases.

A snapshot of the recommendations is in table 5.1.

The recommendations convey that each decision locus, on its own, cannot solve the problem. It will take a coordinated, balanced approach to tackle drug resistance effectively on a global scale (see figure 5.1), supported by strong global leadership. Figure 5.1b shows the consequences of losing any component —especially better information.

Recommendation #1
Improve **surveillance** by collecting and sharing resistance information across networks of **laboratories**

The CGD Drug Resistance Working Group recommends that the global health community establish a multidisease surveillance network to track the emergence and spread of drug-resistant strains of disease and develop data-sharing platforms for multiple audiences, including policymakers and global health donors.

Table 5.1
Old problems and new solutions to global drug resistance

Because . . .	We propose . . .
Drug resistance testing and surveillance capabilities are inadequate	Low-cost formal and innovative informal surveillance to fill the information gap and broaden disease testing with new laboratory technology
Weak points in the supply chain and inappropriate dispensing facilitate drug resistance	Better incentives for accountability from drug and diagnostics manufacturers, prescribers, and dispensers to reduce drug resistance
Drug regulation is weak and uncertain	Strengthening regulators through support to regional networks
There are many ideas to create incentives for R&D for neglected diseases	Stimulating research for resistance-specific technology development

In establishing a multidisease drug-resistance surveillance network, the global health community can build on a range of existing efforts

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, how, and why 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 pharmaceutical markets to enable better disease control, combined with district level information for better patient care.

Making drug-resistance surveillance routine across all societies and for all significant infectious diseases offers substantial benefits. Timely information about pathogen susceptibility will enable better management of patients and infection control in clinical settings. Aggregating the data to the population level will allow for 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 and 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, and procurement by global health initiatives.

Figure 5.2 shows how a global cross-disease drug-resistance surveillance system would draw on the comparative advantages and specific expertise of existing players. With increased investments in the use of basic laboratory technologies, information sharing, and networking, this goal is within reach.

The primary innovation would be to develop and implement new protocols for the collection, recording, and sharing of drug resistance data, with special attention to increasing use of molecular methods as technology becomes more widely available. A first step is to establish sentinel resistance indicators for both high- and low-income settings, and standardize testing across laboratories for each disease. While many vertical disease programs work with their own dedicated lab networks, these labs can be utilized to gather cross-disease drug resistance information.

Figure 5.1
Collective responsibility for preventing drug resistance

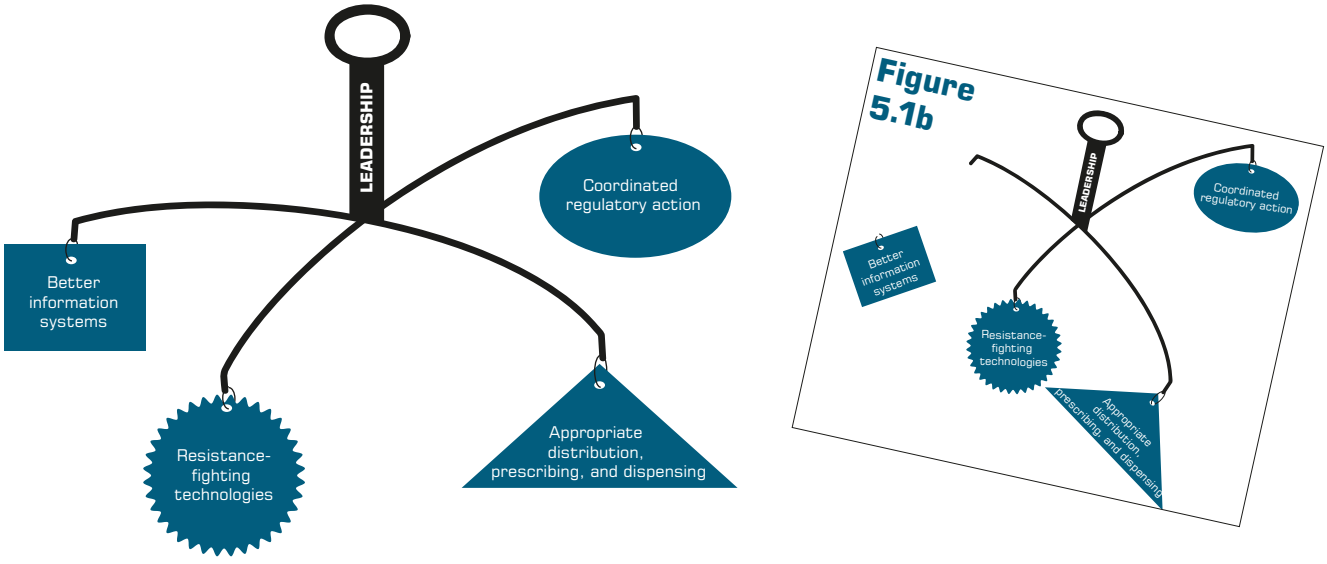
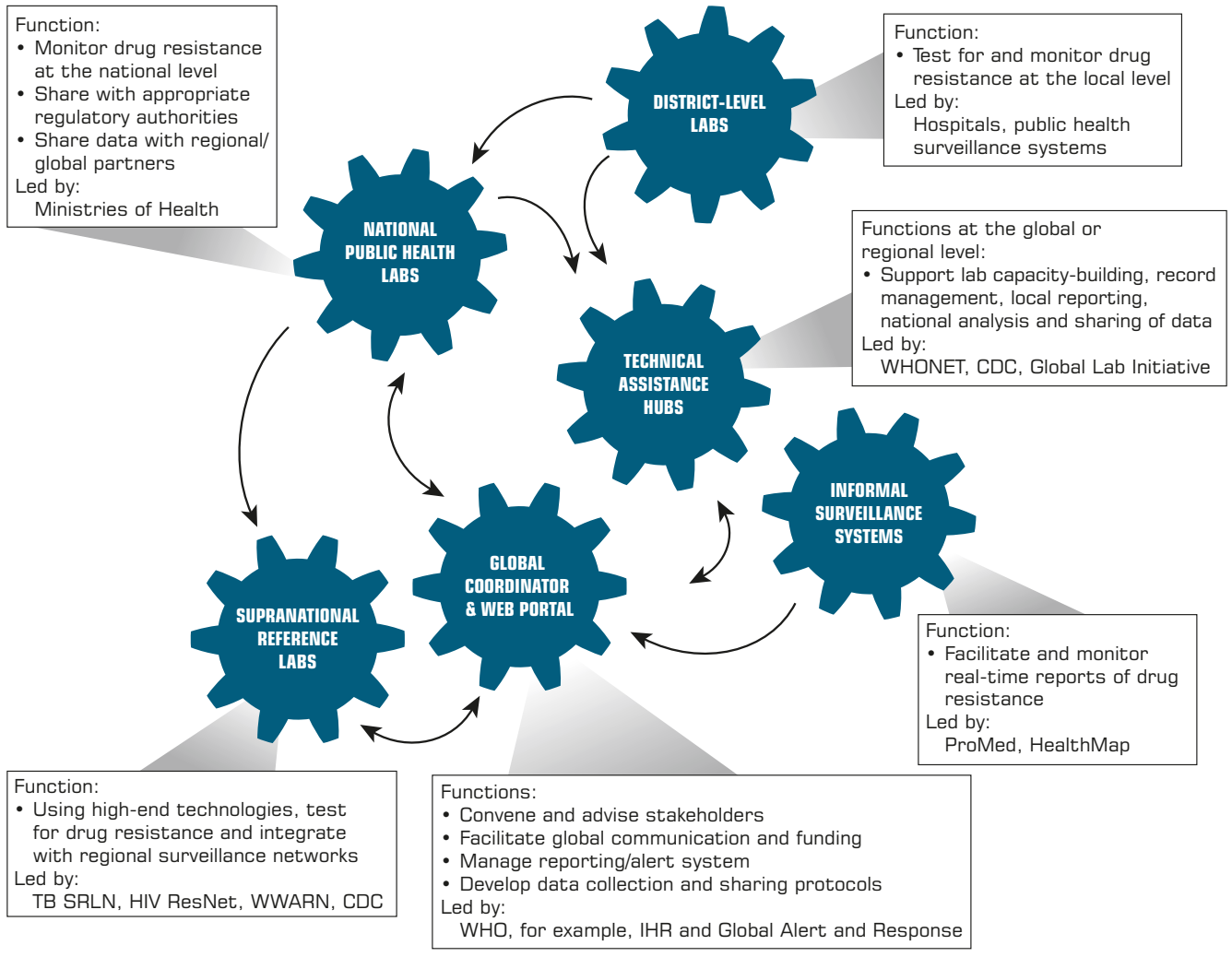


Figure 5.2
An interlocking system for drug-resistance surveillance



There are promising developments on the horizon that could lay the foundations for this system. For example, the IHR team at WHO is planning to expand its new Global Laboratory Directory to include the listing and mapping of laboratories and networks focused on drug resistance.[i] Meanwhile, WHONET Surveillor is being developed, which will have a Web interface. It will also draw on data captured through the use of WHONET software in laboratories across the world to create a global database of drug-resistance data. These information-sharing initiatives must be properly funded (the WHONET team estimates it will take a mere US$1.25 million a year for three years to develop WHONET Surveillor), if they are to make the important and timely contribution they promise. To date, neither has been funded. This represents a substantial missed opportunity in relation to the $23 billion

i. See www.gladmap.org for more information.

per year spent on global health initiatives, including billions of dollars on providing drugs in developing countries.[1]

In establishing a multidisease drug-resistance surveillance network, the global health community can build on a range of existing efforts—but mobilization and coordination are needed to harness their resistance-prevention potential. The PAHO Network described in box 4.1 confirms that even relatively modest funding and technical support can improve coordination of resistance surveillance.

Many of the needed tools and technical functions already exist within designated health organizations—for example, WHONET and CDC on drug-resistance related technical assistance and the Stop TB Global Laboratory Initiative on laboratory capacity building—although some would need additional financial and human resources to operate at the scale demanded by such a system. A significant amount of resources are obtainable through health system strengthening efforts already underway through donors and the World Bank.

First, donors and technical assistance partners must support developing countries in managing patients with drug-resistant forms of disease and in undertaking routine resistance surveillance across diseases. Both can be accomplished by strengthening basic microbiological laboratory services and linking them to public health surveillance systems.[ii] It will be important to ensure that both public and private actors are undertaking coherent and consistent approaches to drug susceptibility testing and related data collection.

Second, existing disease-specific supranational networks focused on resistance surveillance must link with each other to make the best use of scarce capacity, provide opportunities to collaborate in the delivery of training and tools, and allow networks to identify resistance across diseases. Development of common resistance measurement would facilitate better data-sharing across laboratories. Meanwhile, real-time disease surveillance platforms should incorporate drug-resistance data into their efforts.

ii. WHONET is well placed to provide technical assistance in this area. It has developed a free, downloadable software (available in 18 languages) to help technicians in resource-constrained laboratories to record and analyze patient data in order to track patterns of resistance. This supports effective patient care and yields useful trend data to support ongoing drug-resistance surveillance.

Three concrete outcomes can quickly build on an improved drug-resistance knowledge base:

- A Web-based resource center or portal should be developed to bring drug-resistance data together on an ongoing basis and present them in a compelling and accessible format.
- Drawing on these data, a biennial Global Drug Resistance report should be produced to illustrate trends in key resistance indicators within countries and across regions and to monitor actions taken in response.
- WHO needs to clarify how and when the IHRs mandate countries to report the emergence or transmission of drug-resistant forms of disease.

Recommendation #2
Secure the drug **supply chain** to ensure **quality products and practices**

Part A: The CGD Drug Resistance Working Group proposes that an expert technical group, including drug manufacturers, develop a global standard to maintain, monitor, and report on drug quality post-marketing through the International Organization for Standardization (ISO). Publicly funded drug purchasers, whether national governments or international donors, should require compliance with the ISO standard as a criterion of procurement.

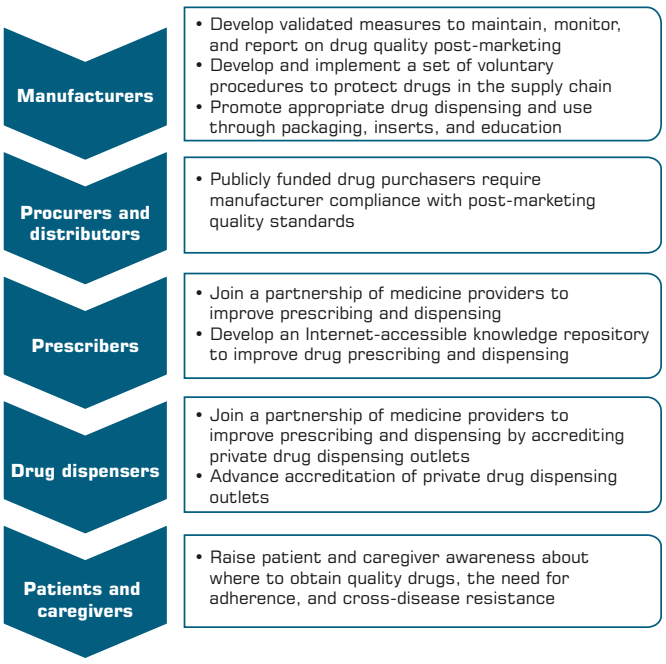
Part B: The CGD Drug Resistance Working Group proposes creation of a new partnership among associations of medicine providers, regulators, and others in the supply chain to improve decisions on drug provision and use. The partnership will promote quality assurance models of drug provision, especially accreditation of dispensers and improved information to consumers.

The pharmaceutical supply chain extends from manufacturers to patients, each step along the way presenting the potential for breaches that contribute to drug resistance. International

standards exist to assure and monitor for quality in the first step of the chain, the manufacturing process. But the next steps—distribution, marketing, and wholesale and retail selling—lack rigorously applied quality standards and regular monitoring. As a result, both the product and the process may become compromised. Drug resistance will be slowed only by optimizing systems in the entire supply chain with the cooperation of the public and private sectors, both upstream and downstream. The World Bank recently demonstrated in a pilot study that "simple but smart" supply chain improvements can be highly effective in improving drug delivery, reducing stock-outs and storage time. These steps in Zambia were estimated to reduce child mortality from malaria by 37 percent.[2]

This recommendation ties together the actors in the supply chain, from manufacturer to drug seller, by proposing transparent, monitored, and meaningful standards that allow drug purchasers, regulators, and patients to differentiate between good- and poor-quality drugs. The recommendation is in two parts: standards for manufacturers and standards for those who prescribe and dispense drugs. Figure 5.3 shows the relationships among the parts of the supply chain addressed in this recommendation.

Figure 5.3
Desired outcomes in the drug supply chain



Part A: Pharmaceutical industry to take greater responsibility for supply chain integrity

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

The ISO certification will help resolve two features of drug markets that currently drive a wedge of uncertainty between producers and consumers. There is information asymmetry about the emergence and spread of resistance to a drug because producers sometimes have knowledge about factors that influence drug resistance, such as how much and where their drugs are sold, and at times perform their own surveys. Little of this knowledge is shared with health officials, regulators, or consumers. Second, the information asymmetry creates a moral hazard, as drug companies have little incentive to reveal the presence of resistance to their products, or other drug quality issues that may put them at a competitive disadvantage in the marketplace.[3] Certification would create a level playing field for companies that comply with the uniform standards. It removes both the wholesale buyers' uncertainty about how to choose among many drug companies and the need for manufacturers to closely guard important information about their products relevant to public health.

The information conveyed by a postmarketing quality ISO certification should induce drug purchasers to be more selective with regard to drug quality, rather than be largely guided by price. On a larger scale, the quality certification should become an important signal to inform the buying decisions of major bulk purchasers of drugs for developing countries—both national governments and donors.

Examples of the types of standards to be included in an ISO certification are in box 5.1. These examples are not meant to be

"Simple but smart" supply chain improvements can be highly effective in improving drug delivery, reducing stock-outs and storage time. These steps in Zambia were estimated to reduce child mortality from malaria by 37 percent

prescriptive, but rather indicative of what pharmaceutical companies could feasibly and cost-effectively do to slow the development of drug resistance down the supply chain. ISO certification would be voluntary, and companies that meet the postmarketing quality standards would demonstrate to purchasers in national and global markets that they monitor the continued quality and effectiveness of their products, engage in measures to encourage good prescribing and dispensing practices, and enable rational medicine use by consumers.

The ISO is not the only way to impose industry standards for drug-resistance prevention, but it has specific merits. It relies on industry involvement and expertise, and thus is credible to drug manufacturers and adaptable to changing technologies and conditions. The ISO uses a voluntary consensus process that defines the technical scope and requirements of its standards. Individual companies then choose whether to become certified and results are monitored annually for compliance at low cost.

Developing new ISO standards can be an arduous process. Existing management standards from ISO provide ways to detect and correct problems in industrial processes.[iii] This might be a useful place to begin designing the processes needed to reduce errors and omissions that lead to drug resistance in the postmarketing segment of the supply chain. With sufficient enthusiasm from the pharmaceutical industry, it might also be an opportunity to align industry interests and actions better with government and public interests to maintain quality drug supplies. Meeting the quality standard will involve some costs, especially for more systematic drug quality testing down the supply chain. But it will also provide essential information for the use of donor agencies, procurers, and regulators and offer the possibility for economies of scale in testing and monitoring.

Drug manufacturers share responsibility with regulatory authorities to provide safe, high-quality drugs and track their continued effectiveness. As with the efforts of regulators, there has tended to be greater emphasis on monitoring drug safety than on quality through international pharmacovigilance efforts.[iv] This recommendation highlights the importance of drug quality, alongside drug safety, and provides a transparent and uniform process to all manufacturers that wish to make and verify their efforts to prevent drug resistance and ensure effective treatment.

Box 5.1
Examples of practices for a drug resistance containment industry standard

- Periodic drug quality and/or product integrity sampling at distribution and point of sale with results made available to health providers, regulators, and the public
- Regular monitoring of supply chain security, including securing products in transit
- Easily understood labeling and local language package inserts that include consumer information about adherence protocols and drug resistance risks
- Elimination of marketing practices that incentivize prescribers and dispensers to select specific brands
- Support for improved prescribing and dispensing practices through independent associations (see Part B of this recommendation for possibilities).

Part B: A global partnership for quality drug dispensing, prescribing, and consuming

At the other end of the drug supply chain from manufacturers are a diverse group of drug providers—among them public, private, formal, and informal providers. They have a range of training and skills—from licensed doctors and nurses to roadside drug sellers. Regardless of their professional status, their access to the tools and practices to discern drug quality and encourage rational use of drugs must be universal. To achieve this, the CGD Drug Resistance Working Group proposes a new ***partnership of medicine providers, regulators, and others in the supply chain*** to provide the knowledge base and access to resources for countries to develop and promote quality assurance models, especially dispenser accreditation, that will reduce harmful practices that lead

iii. Called ISO 9001:2008, this certification is used to improve systems within health care and other sectors.

iv. For example, see http://www.who-umc.org/DynPage.aspx.

to drug resistance. Furthermore, the global partnership would support regional and local partnerships to implement quality assurance and rational use programs.

The partnership would fill several voids that currently face countries seeking to reduce or eliminate weaknesses in their drug supply systems. At the global level, it would:

- Create a **knowledge repository** of tried-and-tested models for improving drug prescribing and dispensing practices in developing countries.
- Develop and test **educational curricula** aimed at improving drug dispensing and rational use.
- Offer a platform through which **technical assistance** to countries on quality drug prescribing, dispensing, and consuming could be accessed.
- Provide **links to financial resources** to adapt experiences from other countries, pilot new models, and implement sound, country-specific interventions.

At the local level, it would:

- Create national multistakeholder groups to adapt the tested models to their country contexts and capacities, led by designated "champion" organizations, such as pharmacy councils.
- Link country efforts to global financial resources.

Details of each of these functions are provided below.

The global partnership would include international health provider professional associations such as pharmacists and nurses; regional WHO offices; the World Bank Group; major global donor agencies such as the Global Fund to Fight AIDS, Tuberculosis and Malaria; and advocacy organizations, such as ReACT and APUA. National chapters of these organizations, implementing NGOs, patient organizations, and national drug regulatory authority involvement will form the core of national partnerships. Patient advocacy groups should become an integral part of these partnerships both at the global and national levels. Multiple stakeholders will help deflect the possibility of "capture" of the partnership and its functions by any single interest.

The global partnership could be implemented immediately through a recently established multidonor consortium of organizations working on the private health sector in developing countries, Harnessing Non-State Actors for Better Health for the Poor, an initiative of which is a collaborative project to establish a Private Sector Health Advisory Facility,[v] anticipated to be hosted at the World Bank Group.

Specific partner roles and responsibilities would be developed by the global partnership, and may include:

1. *A knowledge repository on improving behaviors influencing drug provision*

An Internet-accessible repository of the evidence available from peer-reviewed and gray literature about quality drug prescribing and dispensing would be created and housed within the partnership. Evidence about interventions to improve dispensing would come from WHO (including WHO Collaborating Center on Pharmaceutical Policy), World Medical Association, and other global organizations. Evidence about interventions to improve formal and informal sector dispensing would come from WHO (again including WHO Collaborating Center on Pharmaceutical Policy), International Pharmaceutical Federation, Ecumenical Pharmaceutical Network, Commonwealth Pharmacists Association, International Society of Chemotherapy,[vi] and other experts.[vii]

2. *Educational curricula and tools*

The partnership will actively capture and share existing drug-resistance specific educational resources for formal drug providers through a Web site portal similar to that of the Human Resources for Health Resource Center.[viii] Where appropriate, the partnership will produce or contract out production of additional materials, and could promote Wikipedia-type collaborative development of materials to keep the information dynamic and up to date.[ix] Additionally, given that countries are increasingly making continuing professional development

v. See http://www.cgdev.org/content/publications/detail/1423350 for more information.

vi. The International Society of Chemotherapy is currently in the process of creating a network of sub-Saharan physicians and researchers, including a registry of interventions on drug stewardship and resistance.

vii. For instance, from the USAID-funded Strengthening Pharmaceutical Services project housed at Management Sciences for Health, the Kenya Medical Research Network, and other organizations.

viii. See http://www.hrhresourcecenter.org for more information.

ix. For a health-specific example of such a resource, see MedPedia.

compulsory for professional licensure, the partnership could identify ways to strengthen the capacity of pharmacy councils and professional bodies to provide resistance-specific education for formal dispensers. A variety of educational efforts that target informal dispensers should also be developed and implemented through community health workers and other trusted information sources. These efforts require monitoring from the partnership.

3. *Access to technical assistance*

The partnership will provide developing countries with links to technical assistance provision from appropriate partners, such as those directly involved in accredited drug-dispensing outlet implementation in Tanzania and the International Pharmaceutical Federation's efforts to improve distribution, standards, and practice within the framework of WHO Guidelines for Good Pharmacy Practice. It will also concentrate donor support where there is a defined country plan for sustaining activities, including creating and enforcing penalties through country regulatory and legal systems.

4. *Financial support for piloting country projects*

National partnerships will actively:

- Identify organizations to lead the national partnership and establish measurable milestones of success.
- Develop and pilot location-specific drug resistance educational materials and tools for outreach to providers and consumers.
- Adapt and pilot context-specific models to engage informal private sector drug dispensers in education efforts and accreditation programs, possibly similar to the Tanzanian model described in box 4.5.

This part of the recommendation draws together a wide body of knowledge and expert organizations that have a common interest in improving medicine practice in developing countries and suggests the means to harness that interest to prevent drug resistance. A key aspect of its value is building on what is already known and extending it to new settings.

The elements essential for success include: external support for local implementation at the outset, with incentive toolkits that can be locally adapted; monitoring and inspections with technical oversight through the national partnership, but with public accountability and a threat of government sanctions through legal channels; and information to enable consumers to choose higher-quality drug provision, through accreditation of providers or similar programs, which include provider reimbursement schemes where feasible. Finally, the global partnership would identify key knowledge gaps and facilitate implementation of pilot programs to further determine which combinations of rewards and penalties work best in different settings to improve prescriber and dispenser practices.

Recommendation #3
Strengthen **national drug regulatory authorities** in developing countries

The CGD Drug Resistance Working Group proposes that national and international support be provided to create new regional networks of national drug regulators, enhance existing ones, and develop shared incentives to protect drug efficacy.

NDRAs struggle to protect their populations from unsafe and poor-quality drugs because of their limited resources and the huge challenge of monitoring drug flows within and across their borders. They often focus on enforcing quality manufacturing standards, while neglecting to detect substandard products beyond the factory gate. As a consequence, regulators may have little knowledge about the quality of drugs circulating in their countries and where said products originated. Mutual cooperation can reduce the burden on and increase the impact of NDRAs more effectively than individual capacity building on drug resistance.[x]

A well-functioning, mutually supportive regulatory network will fortify individual NDRAs to achieve greater effectiveness and efficiency. Within a network, countries can inform each other about poor-quality and counterfeit drugs, coordi-

x. Successful regional networks may eventually lead to more broadly harmonized regulatory processes as exemplified by the European Medicines Agency and information sharing as shown in the PAHO Network for Antibiotic Resistance Monitoring.

A well-functioning, mutually supportive regulatory network will fortify individual NRDAs to achieve greater effectiveness and efficiency

nate inspections and border control of drug flows, and build capacity through technical training. A network creates an information hub to understand which drugs are available in different locales and how they work, identify trusted sources of medicines, and standardize formats for sharing information about registered drugs in different jurisdictions. A regional configuration also allows national regulators to align their drug policies better and standardize treatment guidelines with their neighbors.

Regional activities and responsibilities should include:

- Drug-resistance surveillance sharing and cooperation.
- Human resource strengthening, particularly within regulatory agencies.
- Harmonization of quality assurance processes and information sharing about substandard products.
- Alignment of national drug policies and standard treatment guidelines, where appropriate.

Specific terms of reference, mission statements, and staffing should be determined by the distinct needs of the regional networks, and donor priority should be given to the 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.

The Drug Resistance Working Group recommends that regional drug regulatory harmonization efforts currently under way through the New Partnership for Africa's Development (NEPAD) and supported by multiple donors explicitly incorporate drug resistance in their mandate, compatible with the emphasis on regulatory capacity building. The first step is for countries to begin sharing drug quality and resistance monitoring information.[xi]

xi. The Regional Economic Communities in Africa are the locus of current activities on regulatory harmonization in Africa. The main participants are the NEPAD Health Secretariat, WHO-HQ, WHO-AFRO, the Bill & Melinda Gates Foundation, the Clinton Foundation, and DFID. Other developed country agencies are providing technical assistance. Currently under way is feasibility analysis of the scope of activities to be undertaken by regional networks.

Recommendation #4
Catalyze research and innovation to speed the development of resistance-fighting technologies

The CGD Drug Resistance Working Group recommends the creation of a Web-based marketplace to share resistance-specific research and innovation across diseases. This facility would aim to lower the transaction costs of research collaboration and partnership. By helping early-stage scientists to partner with each other, learn together, and link to sources of investment, the marketplace could catalyze innovation and accelerate the development of needed technologies.

The drug resistance technology marketplace would comprise two elements: a Web-based showcase for resistance-related research and innovation, coupled with a brokerage facility. Each entry in the showcase would give information about the innovation, institutions involved in the research, funders, and patents—similar to the approach used by iBridge.[xii] Entries could also be tagged with keywords, enabling them to be easily organized, grouped, and searched. A broker would manage the marketplace, facilitate the networking of researchers in similar areas, and offer advice and technical support to those entering into partnership. This could include the development of model contracts, partnership arrangements, and intellectual property agreements. The broker could also be proactive, matching researchers and developers with public and private investors, such as grant-makers or venture capitalists, and reaching out to developing country researchers to bring them into the marketplace.

Increased drug resistance surveillance and information sharing —as suggested in Recommendation #1—will also contribute to the development of a body of knowledge that will inform R&D for resistance-related technologies. To maximize the opportunities, the marketplace broker would need to explore ways to link with the envisaged drug-resistance Web portal and the surveillance networks feeding into it.

xii. See www.ibridgenetwork.org for more information.

A Web-based marketplace could catalyze innovation and accelerate the development of needed technologies

The marketplace would include research and innovations that contribute to the development of technologies such as new drugs, other infectious disease treatments, and innovative tools to facilitate the rational use of drugs. Examples of relevant technologies include point-of-care diagnostics and rapid drug susceptibility tests, improved drug delivery methods, new classes of therapeutics, fixed-dose combination therapies, and technologies that can be added to drugs to enhance their potency or prolong their efficacy (for example, efflux pump inhibitors and novel excipients).

A major attraction of the marketplace model is its flexibility. It can expand to accommodate new fields of innovation and facilitate networking across different infectious disease communities. It could be combined with more advanced collaborative research tools, such as Collaborative Drug Discovery, thereby enabling researchers to share greater amounts of data with each other if they so choose. It could also be combined with a range of different R&D incentives, such as prize offerings (including those linked to crowdsourcing or open innovation platforms such as NineSigma and InnoCentive) and other incentives that give researchers a market or other reward, or grant-making facilities and other incentives that offset some of the costs or risks of research. Finally, the showcase approach lends visibility to a broad range of innovations, some of which will have strong commercial viability and relevance to established pharmaceutical markets. Others will be more relevant to emerging or underserved pharmaceutical markets. If more tightly managed approaches to R&D are needed to advance the latter, mechanisms such as PDPs might "spin off" from the marketplace.

All interested parties stand to gain through the marketplace. On the "supply" side, the marketplace would act as a platform for early-stage researchers to share their knowledge of and work on resistance-relevant technologies virtually, as a way to advance their development through collaboration. Initially, it is likely that most contributors will come from public sector labs—academic and government—and nonprofit research organizations. With a strong incentive to get their innovations known and to help propel them out of the lab and across the technology transfer "valley of death," such players have traditionally been early adopters of these types of initiatives. When activity increases enough to achieve a critical mass, smaller companies, many of which have recently been spun out of academic labs themselves, are likely to follow.

On the "demand" side (which includes those wishing to find new technologies to develop and market), later-stage biopharmaceutical companies, venture capitalists, and foundations or public funders (such as the U.S. National Institutes of Health or the UK's Wellcome Trust) could use the marketplace as a one-stop-shop to decrease significantly the transaction costs of evaluating innovations or discoveries that may be worth in-licensing, funding, or otherwise linking to. There may also be potential for marketplace users to gain preferential access to demand-side partners that can help commercialize strong candidates.

The incentive for reduced transaction costs is already apparent in recent industry activities. In June 2009, Eli Lilly & Company announced the launch of its Phenotypic Drug Discovery initiative.[4] The project is similar to the type of marketplace the Working Group is calling for, except that it focuses on adding to the company's profitable pipeline diseases—cancer, Alzheimer's, osteoporosis, and diabetes—and, of course, Eli Lilly & Company retains control of the entire process, with first rights to a licensing deal. While such company-led initiatives may proliferate for noncommunicable diseases in the future, the resistance marketplace will continue to add value, given its relevance to a wide range of resistance-specific technologies and across many different infectious disease areas and markets.

Whether as a result of necessity, improved technological capacity, or evidence of collaborative research productivity, the trend in recent years has been towards increasing information sharing and collaboration in the product development arena. Creating a virtual marketplace for resistance-relevant technologies is consistent with this movement and has the potential to catalyze R&D efforts for much needed innovations by giving them profile, promoting networking and collaboration, and decreasing transactions costs. In the long term, such innovation will help address both the lack of new products in the pipeline to defend against ever-evolving microbes and the misuse of the products that we do have, thereby helping us to limit the emergence and spread of drug resistant forms of disease.

Notes

1. Ravishankar et al. (2009).
2. World Bank (2010).
3. Yadav (2009).
4. "Eli Lilly and Company Announces New Drug Discovery Initiative." June 15, 2009. http://newsroom.lilly.com/releasedetail.cfm?ReleaseID=389589.

6
Conclusions

Chapter at a glance

- Key actors at both global and country levels have yet to accept responsibility for addressing the challenge of drug resistance.
- A global health architecture for drug resistance—laws, regulations, institutions, governance mechanisms, systems, and tools—is needed to foster a sense of collective responsibility to protect drug efficacy.

We have the means to turn back the threat of drug resistance

Recent years have witnessed the publication of several global health reports on drug resistance, each containing many recommendations for action. The World Health Assembly passed resolutions on antimicrobial resistance in 1998, 2005, and again in 2007. And yet, the global health community has not prioritized the issue, and the extent of action within countries—particularly in resource-constrained settings—is extremely limited relative to the scale of the challenge. This reflects an accountability gap: key actors at both global and country levels have yet to accept responsibility for addressing the challenge of drug resistance.

Collective responsibility is needed. But how can it be developed? Certainly, we must make it easier for all actors to behave responsibly, including by building their capacity and giving them the information they need to act. We should also make it harder for actors to neglect their stewardship role, through the development of appropriate standards and regulatory instruments. And global leaders must send strong and consistent signals about the importance of the agenda.

In short, we need a global health architecture for drug resistance—laws, regulations, institutions, governance mechanisms, systems and tools—that fosters a sense of collective responsibility to protect drug efficacy, thereby "opening the space" for action by national and local actors. Systems of mutual accountability—such as regional networks and IHRs—need to be strengthened and more widely used.

Drug resistance is present across the world. It will not be solved at the patient's bedside, although infection control in clinical settings is an essential life-saving step. We cannot afford to be indifferent to the spread of resistance. We do not and will not for the foreseeable future have enough effective drugs to control resistant pathogens if they become the norm. We urgently need to find new solutions, scale up solutions that work, and show far greater leadership if we are to make headway against infectious diseases.

We have the means to turn back the threat of drug resistance. The steps recommended by the Working Group will help to preserve the efficacy of our global drug supply. Now, coordinated, collective action is needed to bring the recommendations to fruition. Those who are in a position to determine our future treatment choices should be called upon to explain how they are responding.

Donors and philanthropic organizations need to ensure that their laudable efforts to increase access to drugs in the developing world are accompanied by measures to protect the continued effectiveness of drug treatment. They must strenuously enforce quality standards throughout the supply chain, ensure that adequate knowledge is gathered about the effectiveness of the medicines they are providing, and use their purchasing power to drive drug quality standards throughout the supply chain.

Governments have a responsibility to provide regulation and oversight of drug licensing, manufacturing distribution, and use, as well as to properly support laboratory facilities and surveillance systems to detect and monitor drug efficacy. Improved or new regional regulatory agencies will allow governments to align drug policies and accomplish more with existing resources. Developed country governments should aggressively fight drug resistance both to protect the health of their own citizens and to ensure global health goals are met. It should be core to health system strengthening. Two immediate steps are to expand the new U.S.-E.U. Task Force on Antimicrobial Resistance into a global task force, and to promote Antibiotic Resistance Day on November 18 throughout the world.

Companies that develop and manufacture drugs and other medical technology have a responsibility to ensure that their life-saving products are safe and effective, and remain so. A set of industry standards to ensure post-marketing quality would reduce the circulation of poor-quality drugs and discover weaknesses in drug supplies before they reach patients.

Global health institutions must make drug resistance a priority —across all treatable diseases—by providing financial and technical support to developing nations to meet and maintain standards, and clearly articulate countries' responsibilities regarding resistance under the global health legal framework. WHO should reverse almost a decade of neglect of antimicrobial resistance.

Patients, *prescribers*, and *dispensers* must all gain greater awareness of the personal and social costs of drug resistance, and employ far greater diligence in appropriately using drugs.

We can no longer afford to be indifferent to the spread of drug-resistant diseases. We must shows collective leadership if we are to meet this challenge. For the sake of all people who deserve life-saving care when their health is imperiled, now and in the future, drug resistance must be addressed urgently and aggressively as a global health priority.

Appendixes

Appendix A

Needed research to support a global response to drug resistance

This report offers recommendations for policy and actions in areas that are central to any global effort to curtail drug resistance. By necessity, the CGD Working Group on Drug Resistance made difficult choices to study and recommend action only on selected aspects of the problem of drug resistance. We focused on problems created by market and institutional failures where we had adequate expertise, and where the evidence for successful action is strong. We declined to devote substantial attention to several other aspects of drug resistance, either because the data and evidence needed to understand them were missing and could not feasibly be obtained within the time and resource constraints of this project, or because other reputable organizations are tackling those issues. Falling into those categories are several crucial issues that need to be better understood, and we urge that public and private resources be devoted to research that will eventually inform a more solid policy approach to the full range of drug-resistance risks.

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 because of definitional and methodological variation. The literature is dominated by studies from developed countries and is disease- and drug-specific.[i] In spite of the very limited data, an assessment of the economic costs of resistance must be made available to global and national policymakers and donors. Data on costs, mortality, and morbidity associated with drug resistance are vital to allow policymakers and donors to give appropriate priority to resistance. Because costs in developing countries are vastly different from those in rich countries, this report does not provide a full discussion of the existing literature. We urge the World Bank and other global funders of drug treatment to support rigorous analysis of the social costs of drug resistance. To evaluate the results of recommendations made above, information is needed to ascertain the costs of resistance and the benefits derived from protecting drug efficacy more rigorously.[ii]

Research is needed to investigate the effects of using therapeutic drugs as prophylaxis. The use of drugs as prophylaxis—that is, to prevent the transmission of disease or its development in an uninfected 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 to the use of emergency postexposure prophylaxis with ARVs for women who have been raped. Sometimes the same drug is used for both treatment and prophylaxis, as oseltamivir (Tamiflu) was during the 2009 H1N1 influenza pandemic. A cross-disease example is the use of doxycycline, an antibiotic used to treat a range of conditions (including sexually transmitted diseases, acute respiratory infections, and various gastrointestinal conditions), which 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.[1] 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 on prophylaxis and drug resistance is thin, and the conditions governing the emergence of resistance in specific populations are not well understood.

i. Some initiatives are working to generate and compare information on the burden of disease and costs attributable to resistant pathogens in high-income countries. One example from Europe is https:www.eu-burden.info/.

ii. Supported by the Gates Foundation, the Alliance for the Prudent Use of Antibiotics is conducting pilot studies to collect and analyze economic data on antimicrobial resistance in a limited set of countries.

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 across diseases 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 and agriculture in developing countries, particularly across Africa. The relationship between the use of antibiotics in food animals and plants and patterns of drug resistance in humans is not well understood, but limited data from developed countries have begun to paint a dreadful picture. An estimated 60 percent of diseases that impact humans come from animals,[2] and worldwide, 50 percent of antibiotics go to pigs, chickens, and cows.[3] In the United States, where 35 million pounds of antibiotics were used in 2008, the number jumps to 70 percent.[4]

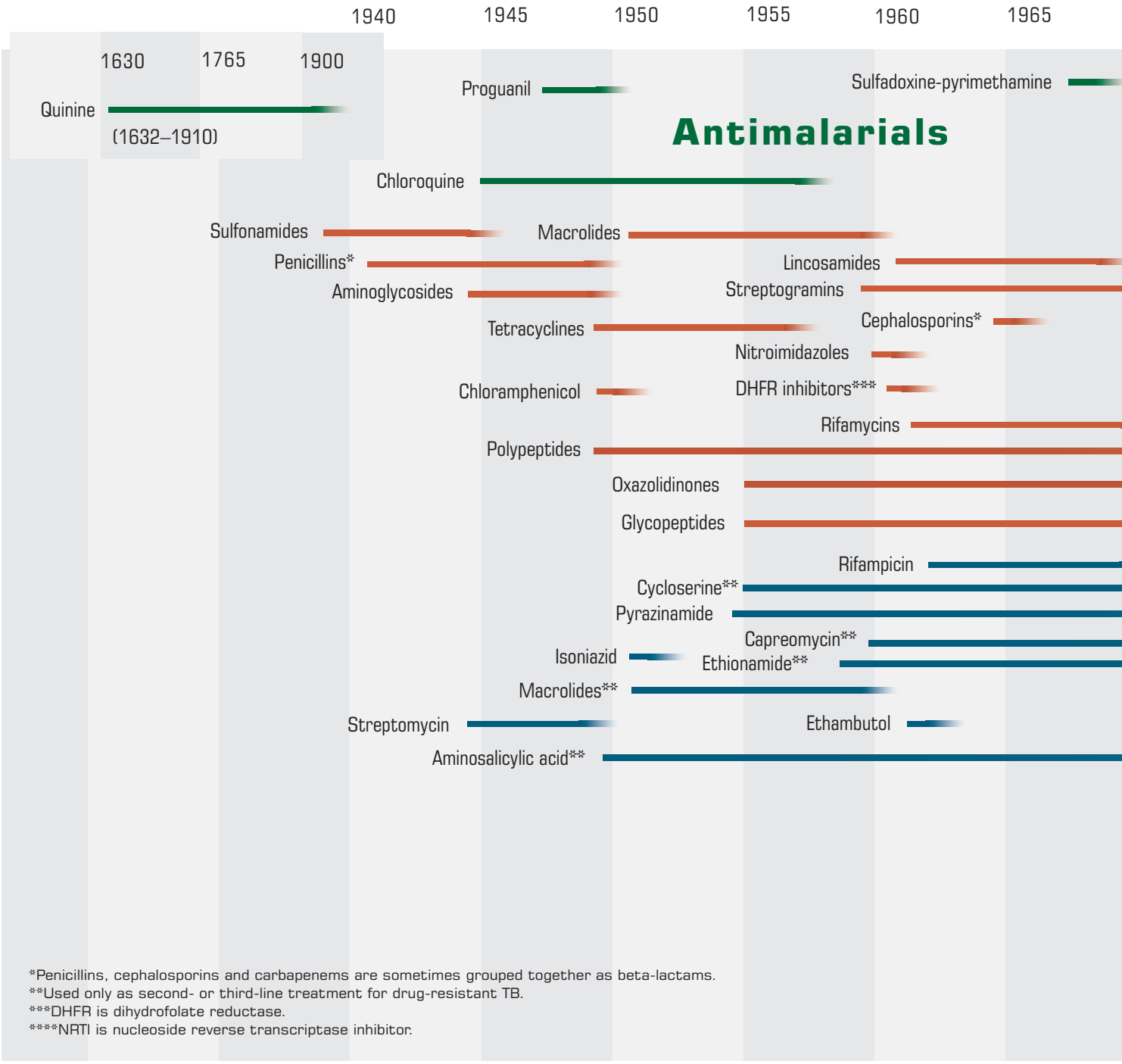
While only modest data exist on developing country use of antibiotics in agriculture, far less research has been undertaken on the impact of this agricultural and veterinary drug use on drug resistance in developing countries. A first step in any research program must be to ascertain the full extent of antibiotic use in food animals, fisheries, grains, and plants in developing countries across Asia, Latin America, and particularly Africa. A systematic review of the literature documenting the presence of antibiotic-resistant microbes in animal feed, carcasses, and meat and milk 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.

Notes

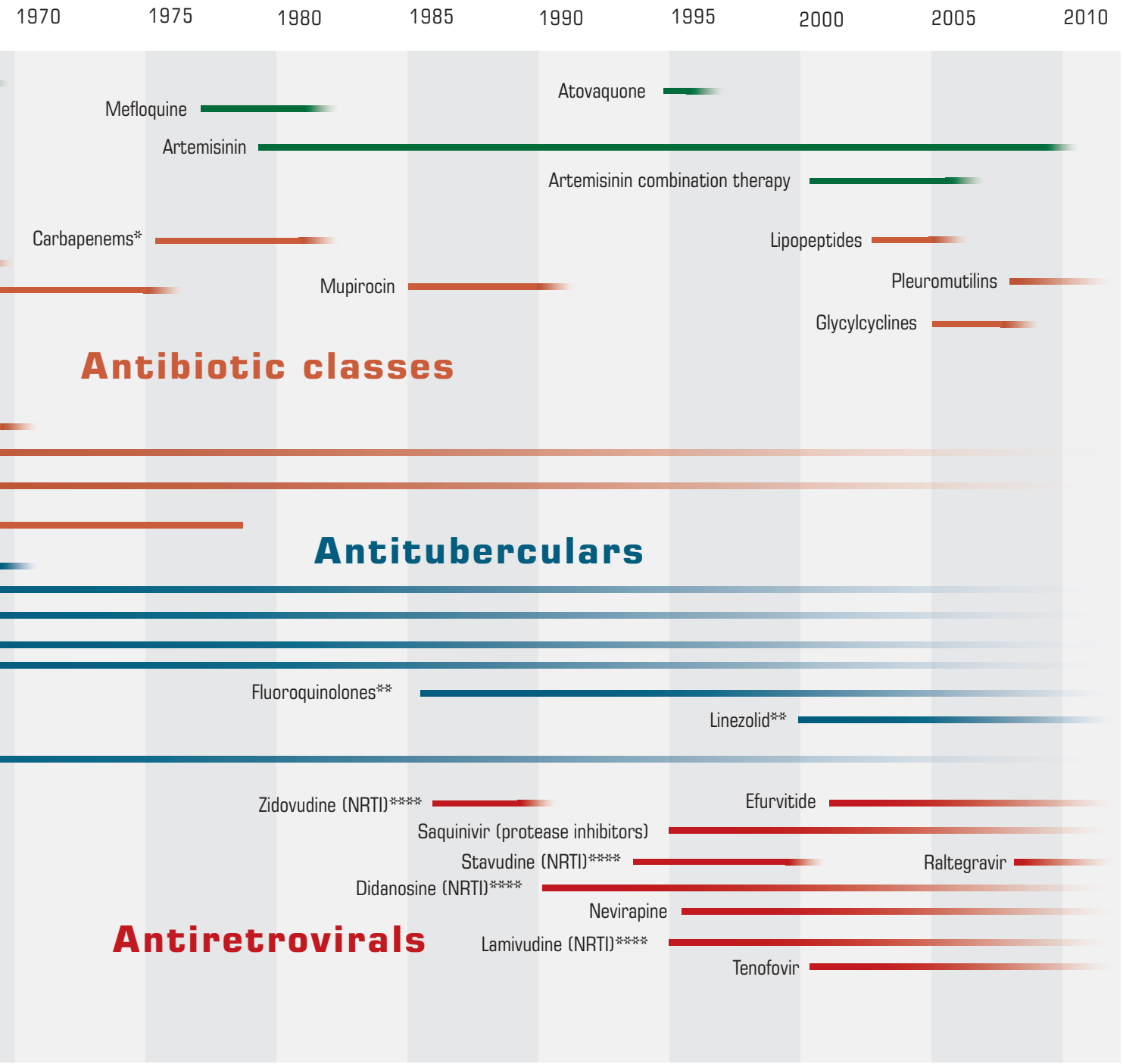
1. Eichner et al. (2009); Hamer and Gill (2008).
2. International Food Information Council Foundation. http://www.foodinsight.org/Resources/Detail.aspx?topic=Animal_Antibiotics_and_Food_Safety_What_you_Should_Know. Accessed March 31, 2010.
3. WHO (2002).
4. *Associated Press* (2009); Mellon, Benbrook, and Benbrook (2001).

Appendix B

Timing of market introduction and emergence of resistance for selected drugs



*Penicillins, cephalosporins and carbapenems are sometimes grouped together as beta-lactams.
**Used only as second- or third-line treatment for drug-resistant TB.
***DHFR is dihydrofolate reductase.
****NRTI is nucleoside reverse transcriptase inhibitor.


1970
1975
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2000
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2010
Atovaquone
Mefloquine
Artemisinin
Artemisinin combination therapy
Carbapenems*
Lipopeptides
Mupirocin
Pleuromutilins
Glycylcyclines
Antibiotic classes
Antituberculars
Fluoroquinolones**
Linezolid**
Zidovudine (NRTI)****
Efurvitide
Saquinivir (protease inhibitors)
Stavudine (NRTI)****
Raltegravir
Didanosine (NRTI)****
Nevirapine
Antiretrovirals
Lamivudine (NRTI)****
Tenofovir

Appendix C

Background and objectives of the Drug Resistance Working Group

The Center for Global Development's Drug Resistance Working Group 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. The Working Group's recommendations encourage actions that help balance society's current and future health care needs with the drugs and technologies available.

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 comprehensive to adequately address the problem. To ensure that all perspectives were given an equal voice, membership consisted of experts from every relevant sector 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), nonprofits, multilateral organizations, NGOs, and foundations. Equally important, we included members from developing countries, in order always to stay firmly grounded in the realities faced by resource poor nations and health systems. A complete list of Working Group members, with short biographies, is in appendix D.

Members of the Working Group were invited to join in a personal capacity and on a voluntary basis. This report reflects a consensus of the Working Group members and does not necessarily represent the views of the organizations with which the Working Group members are affiliated.

Funding for Working Group meetings, analytic work, and consultations was provided under a grant from the Bill & Melinda Gates Foundation.

Appendix D

Profiles of Drug Resistance Working Group members

Emma Back, Technical Advisor to the CGD Drug Resistance Working Group, is a freelance consultant based in New York. Ms. Back also provides technical, policy and communications advice and services to range of other clients, including the UK Department for International Development (DFID), the Medicines Transparency Alliance and UNICEF UK. Until the end of 2005, Ms. Back was a senior civil servant at the UK Department of Health. This followed seven years at DFID, where Ms. Back worked on a wide range of development agendas from access to medicines to global environmental issues. She has a bachelor's degree from the University of Oxford and a master's with distinction in Environment and Development from the School of Oriental and African Studies in London.

Dr. Ted Bianco is Director of Technology Transfer at the Wellcome Trust with responsibility for the promotion of early stage R&D through translational research funding and the management of intellectual property arising from Wellcome Trust-sponsored research. Dr. Bianco has 25 years of experience in biomedical research, specializing in tropical medicine and infectious disease. He obtained his PhD at the London School of Hygiene and Tropical Medicine and subsequently worked at the Walter and Eliza Hall Institute in Melbourne, Imperial College of Science, Technology and Medicine in London and the Liverpool School of Tropical Medicine, where he was the Walter Myers Professor of Parasitology. He joined the Wellcome Trust in 1999 as head of the Centres and Major Initiatives department. Ted is an honorary visiting professor of the Liverpool School.

Nancy L. Blum, MPH, is Vice President, Program Development for Accordia Global Health Foundation. In this capacity she focuses on expanding Accordia's work in training initiatives for malaria case management in partnership with the Infectious Diseases Institute, Makerere University, in Kampala, Uganda. Before Accordia she spent 10 years with the U.S. Pharmacopeia (USP) working in international affairs and leading USP's cooperative agreement with USAID to do system strengthening with national drug regulatory authorities in Africa, Asia and Latin America. Her focus there was on improving capacity for quality control of medicines. Before that she worked for 10 years with Care, 3 of which were in Bangladesh, where she developed a national disaster preparedness plan and managed programs in rural infrastructure development. At Care headquarters in New York City she was Director, Disaster Preparedness Unit, and worked on the ground in Turkey during the initial response to aid the Kurdish refugees from Iraq following the Persian Gulf War. Before that she was Director, Development Education, creating programs for American audiences about global interdependence. Ms. Blum received a master's in Public Health Degree from Columbia University.

Dr. Joanne Carter is the Executive Director of RESULTS/RESULTS Educational Fund (REF), a grassroots advocacy organization with chapters in more 100 U.S. communities and affiliates in half a dozen countries whose goal is to generate the public and political will to end the root causes of poverty. RESULTS works with key administration and congressional allies, partner organizations and technical agencies orchestrating campaigns to tackle major diseases of poverty, increase access to education, expand economic opportunity for the poorest and reform World Bank and International Monetary Fund policies. REF is the secretariat for Advocacy to Control Tuberculosis Internationally, a global network of advocates working to mobilize financial resources and overcome key policy constraints for the expansion of effective TB treatment. Before becoming Executive Director, Dr. Carter oversaw RESULTS' international legislative agenda. She serves as a member of the board of the Global Fund to Fight AIDS, TB and Malaria Board representing developed country NGOs, is a founding board member of Global Action for Children and was the founding chair of the

Advocacy, Communications and Socialization Working Group of the Stop TB Partnership.

Dr. Gail H. Cassell is vice president of Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases at Eli Lilly and Company, where she plays a pivotal role in establishing Eli Lilly's philanthropic Multidrug Resistant TB Partnership and in leading the Eli Lilly TB Drug Discovery Initiative. She has also been intimately involved in the establishment of science policy and legislation related to biomedical research and public health. Dr. Cassell is the former Charles H. McCauley Professor and chair of the Department of Microbiology at the University of Alabama Schools of Medicine and Dentistry at Birmingham. She currently is a member of the NIH Science Management Review Board and the Advisory Council of the Fogarty International Council of NIH. She is a member of the Executive Committee of the Visiting Board of Columbia University's School of Medicine and serves on the Advisory Councils of the Hopkins School of Nursing and University of North Carolina's School of Public Health. She is serving a second term on the Institute of Medicine's Council of the National Academy of Sciences. Dr. Cassell has served on several editorial boards of scientific journals and has authored more than 250 articles and book chapters. She obtained her bachelor's from the University of Alabama in Tuscaloosa and in 1993 was selected as one of the top 31 female graduates of the 20th century. She received her doctorate in microbiology from the University of Alabama at Birmingham and was selected as a 2003 Distinguished Alumnus. Dr. Cassell has received national and international awards and an honorary degree for her research in infectious diseases.

Dr. John Chalker is a UK-trained physician with a PhD in Health Systems Research. He is the current Coordinator of the International Network for the Rational Use of Drugs (INRUD), is a Principal Program Associate with Management Sciences for Health and is Coordinator of a five-year Swedish-funded program to learn how to monitor and improve adherence to antiretroviral medicine in East Africa. He has 22 years of experience in designing, implementing and managing health development projects and quality improvement interventions in a wide range of resource-poor countries in Africa, Asia and the Middle East.

Dr. Alexander Nii Oto Dodoo is a Senior Research Fellow and the Acting Director at the Centre for Tropical Clinical Pharmacology & Therapeutics of the University of Ghana Medical School. He is also the Director of the WHO Collaborating Centre for Advocacy and Training. Dr. Dodoo worked as a Senior Scientist at Roche Discovery Welwyn, UK, from 1996 to 1998 and as a community pharmacist in England in 1999. He is a member of several local and international organizations and societies in the area of drug safety. He is the President of the International Society of Pharmacovigilance and President of the Pharmacy Information Section of the International Pharmaceutical Federation. He is also the current President of the Pharmaceutical Society of Ghana. He is a member of the WHO Advisory Committee on the Safety of Medicinal Products, the CIOMS/WHO Working Group on Vaccine Pharmacovigilance and several data and safety monitoring boards. Dr. Dodoo is the Safety Task Team Leader for the Gates-funded INESS project on the Safety and Effectiveness of Antimalarials. Dr. Dodoo received a B Pharm degree from the University of Science and Technology, Kumasi, Ghana, and a MSc and PhD at the Department of Pharmacy at King's College, London. He is a Fellow of the West African Postgraduate College of Pharmacy Practice.

Dai Ellis is the Executive Vice President of Access Programs at the Clinton Health Access Initiative (CHAI), where he leads the foundation's work on improving the marketplace for HIV/AIDS and malaria drugs, diagnostics and other essential commodities. Mr. Ellis manages the foundation's relationships with

both innovators and generic manufacturers and has negotiated agreements with companies across Asia, Europe, North America and the Middle East. Before his work at CHAI, Mr. Ellis worked at McKinsey and Company serving clients in the pharmaceutical and biotechnology industries. He later joined the Center for Global Health and Economic Development at Columbia University under Dr. Jeffrey Sachs. His work at Columbia took him to Rwanda, where he worked as the advisor to the Director of the National AIDS Commission and helped to launch a national HIV/AIDS prevention and treatment program. While in Rwanda, he also co-founded Orphans of Rwanda, a nonprofit organization that provides university scholarships to orphans and other vulnerable youth. Mr. Ellis is a graduate of Yale Law School.

Dr. Susan Foster is Director of Public Policy and Education at the Alliance for the Prudent Use of Antibiotics in Boston. She has a PhD in health economics from the London School of Hygiene & Tropical Medicine and has a background in pharmaceutical policy. Dr. Foster worked as an economist in Geneva with the WHO Essential Drugs Programme and with the World Bank's Population, Health and Nutrition Department. She has authored numerous publications on infectious diseases and pharmaceuticals, particularly dealing with economic and policy issues. Her research skills and experience are both qualitative and quantitative, including cost-effectiveness and cost-benefit analysis. She also holds an appointment as Professor of International Health at Boston University School of Public Health.

Fred Goldberg is a Principal and Director of Saltchuk Resources, Inc., a diverse group of maritime and related businesses. Saltchuk Resources is one of the 20 largest privately held companies in Washington State with more than 6,000 employees and more than 20 operating sister companies. Mr. Goldberg has extensive experience in the banking industry and as an owner/operator of small businesses. He is also the Managing Partner of Goldberg Investments, operating in Olympia, Washington, as well as Chairman of the Board of Gibbons Lane Vineyard and Winery in Tenino, Washington. He contributes to numerous public and charitable organizations and holds board membership on the Civil Service Commission, Key Bank, St. Peters Health Foundation, Columbia Bank and Panorama City. Mr. Goldberg graduated from the University of Washington with a degree in business administration. In 2005, he co-authored an article in *Nature* on antibiotic R&D and profits.

Martha Gyansa-Lutterodt is a pharmacist, health policy analyst and health manager with extensive experience in initiating, managing, monitoring and evaluating health sector reforms. She is the Head of Ghana National Drugs Programme at the Ministry of Health. Mrs. Gyansa-Lutterodt is an expert in health sector policy dialogue with significant experience in dealing with stakeholders such as product and practice regulators, academics, and researchers. She managed the introduction of a national drug policy in Ghana and coordinated the production and dissemination of two editions of Ghana's Standard Treatment Guidelines and Essential Medicines List. Mrs. Gyansa-Lutterodt managed, coordinated and was involved in most surveys in the pharmaceutical sector in Ghana. She has vast experience in training in both the public and private sectors, including the media in promoting rational use of medicines in Ghana. As one of the drafters of Ghana's Health Policy, she believes in moving health policies into practice that provides sustainable outcomes, especially for the most vulnerable. Mrs. Martha Gyansa-Lutterodt sits on the National Institute for Clinical Excellence International Board and has co-authored several publications in *Global Health*, *International Journal for Risk and Safety in Medicines* and others.

Dr. Gerald Keusch is a professor of international health and medicine at Boston University. He is also an Associate Director of the National Emerging Infectious Diseases Laboratory

Institute and Special Assistant to the President of Boston University for Global Health. Before his appointment at BU, Dr. Keusch served as Director of the Fogarty International Center at the National Institutes of Health and Associate Director for International Research in the office of the NIH Director. A graduate of Columbia College and Harvard Medical School, he is board-certified in Internal Medicine and Infectious Diseases. He was previously Professor of Medicine at Tufts University School of Medicine and Senior Attending Physician and Chief of the Division of Geographic Medicine and Infectious Diseases at the New England Medical Center in Boston. His research has ranged from the molecular pathogenesis of tropical infectious diseases to field research in developing countries. Dr. Keusch is the author of over 300 original publications, reviews and book chapters, and he is the editor of eight scientific books. He is a member of the Institute of Medicine of the U.S. National Academy of Sciences' Institute of Medicine, and presently involved in international health research and policy with the World Health Organization and the Tropical Diseases Research Programme.

Dr. Ruth Levine is a health economist with more than 15 years' experience working on health and family planning financing issues in East Africa, Latin America, the Middle East and South Asia. She is the Director of Evaluation, Policy Analysis & Learning at USAID, where she is working to strengthen the agency's ability to learn from program implementation and to link the best available evidence to decision-making for greater effectiveness and better informed policy. Before joining USAID in March 2010, Dr. Levine served as Vice President for Programs and Operations and was a Senior Fellow at the Center for Global Development. Dr. Levine has also worked at the World Bank, where she designed, supervised and evaluated health sector loans, and at the Inter-American Development Bank, where she served as the adviser on the social sectors in the Office of the Executive Vice President. Dr. Levine holds a doctoral degree from Johns Hopkins University, has published on health and family planning finance topics, and is co-author of *Millions Saved: Proven Successes in Global Health* (CGD, 2004) and *Performance Incentives for Global Health: Potential and Pitfalls* (CGD, 2009). She is the author of several major reports, including *Making Markets for Vaccines: Ideas to Action* (CGD, 2005), *When Will We Ever Learn? Improving Lives through Impact Evaluation* (CGD, 2006), *Girls Count: A Global Investment and Action Agenda* (CGD with the Population Council and International Center for Research on Women, 2008) and *Start with a Girl: A New Agenda for Global Health* (CGD, 2009).

Dr. Rachel Nugent (Chair) has 25 years of experience as a development economist, managing and carrying out research and policy analysis in the fields of health, agriculture and the environment. Before joining CGD, Dr. Nugent worked at the Population Reference Bureau, the Fogarty International Center of the U.S. National Institutes of Health and the United Nations Food and Agriculture Organization. She also served as associate professor and chair of the economics department at Pacific Lutheran University in Tacoma, Washington. Dr. Nugent's publications include a range of topics, from the cost-effectiveness of noncommunicable disease interventions and health impacts of fiscal policies to impacts of microcredit on the environment in developing countries and economic impacts of transboundary diseases and pests.

Dr. Paul Nunn is Coordinator of the World Health Organization unit in the Stop TB Department concerned with Operations and Coordination. He is responsible for coordinating TB control efforts throughout the WHO system and with partner agencies. Previously Coordinator for TB/HIV, anti-TB drug resistance, infection control, and laboratory strengthening, Dr. Nunn led a team that coordinated the global response to XDR-TB. His

team wrote the WHO policies on TB infection control, new diagnostic technologies, and collaborative TB/HIV activities, as well as a number of WHO guidelines on how to address the problem of the impact of HIV on TB. He coordinated the production of the first, third, and fourth WHO/IUATLD global anti-TB drug resistance surveillance reports. Previously, in the Global TB Programme of WHO he was Chief of TB Research and Surveillance in which he set up the Global TB Research Initiative and established the anti-TB drug resistance surveillance project. Dr. Nunn has worked at the London School of Hygiene and Tropical Medicine and the University of California, Berkeley. In addition, he spent time in Kenya researching the impact of HIV on TB in Nairobi. He trained as a respiratory physician at the Royal Postgraduate Medical School, London, following clinical studies at University College, London, and a degree in Physiological Sciences at Oxford University. Dr. Nunn was the Mitchell Lecturer at the Royal College of Physicians, London in 2009 and has published over 100 peer-reviewed papers.

Dr. Iruka N. Okeke is Associate Professor of Molecular Microbiology at Haverford College, Pennsylvania, and a 2010 Fellow of the Wissenschaftskolleg (Institute for Advanced Study), Berlin. She trained in pharmacy and microbiology at Obafemi Awolowo University, Ile-Ife, Nigeria, and at the University of Maryland. Since then, she has continued to research bacterial antimicrobial resistance in West Africa, most recently as a Branco Weiss Fellow of the Society in Science, Switzerland, in collaboration with investigators in Nigeria and Ghana. She has served as a consultant on antimicrobial resistance to the Alliance for Prudent Use of Antibiotics, the U.S. Centers for Disease Control and Prevention, the United States Pharmacopoeia and the World Health Organization.

Kevin Outterson is an Associate Professor of Law at Boston University, where he directs the Health Law Program. Professor Outterson's research focuses on intellectual property and other legal issues relating to global pharmaceutical markets. He is also the principal investigator for a Robert Wood Johnson Foundation project examining the legal ecology of drug resistance. His research articles can be found at www.ssrn.com/author=340746.

Dr. Mead Over is a Senior Fellow at the Center for Global Development researching economics of efficient, effective and cost-effective health interventions in developing countries. Much of his work since 1987—first at the World Bank, where he rose to the level of Lead Economist, and now at the CGD—is on the economics of the AIDS epidemic. After work on the economic impact of the AIDS epidemic and on cost-effective interventions, he co-authored the World Bank's first comprehensive treatment of the economics of AIDS in the book, *Confronting AIDS: Public Priorities for a Global Epidemic* (1997, 1999). His most recent book is entitled *The Economics of Effective AIDS Treatment: Evaluating Policy Options for Thailand* (2006). Dr. Over taught health and development economics, applied microeconomics and econometrics as an Assistant Professor of Economics in the Department of Economics and the Center for Development at Williams College for six years, and as an Associate Professor of Economics at Boston University for five years. He holds a PhD in economics from the University of Wisconsin, Madison.

Dr. Eddie Power, PhD, MBA, has served as the Global Medical Director for Cubist Pharmaceuticals since 2008, working internationally in collaboration with alliance partners to develop medical affairs strategies and plans with Cubist's anti-infective portfolio. Before joining Cubist, Dr. Power was the Therapy Area Head of Anti-Infectives/Virology/Addiction Medicine in Global Medical Affairs at Schering-Plough. He was previously with Bayer Healthcare, where he was Director of Global Scientific Affairs, Anti-Infectives, responsible for global opinion leader interactions, scientific communications, and overseeing

a corporate antimicrobial stewardship program. Prior to joining Bayer in 2002, he was the Director for Strategic Microbiology (Europe & International) at GlaxoSmithKline, working on strategic initiatives to support GSK's anti-infective portfolio. Dr. Power previously held a faculty position at United Medical & Dental Schools, Guy's & St. Thomas Hospitals, London, UK. He gained his PhD from the University of Wales College of Cardiff, UK and MBA from Henley Management College, UK. He is a past recipient of the WH Pierce Memorial Prize (UK) for an outstanding contribution to microbiology.

Dr. Andy Ramsay, MSc, PhD, is a microbiologist and public health expert with more than 25 years' experience in health research and service delivery in low- and middle-income countries. He currently heads tuberculosis diagnostics research at TDR (the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases) in Geneva, Switzerland. He has been Secretary of the Stop TB Partnership's Working Group on New Diagnostics since 2006 and is co-editor of the Web site www.tbevidence.org. He previously held positions at the Liverpool School of Tropical Medicine and at Oxford University's Tropical Medicine Research units in Thailand and Laos.

Dr. Renee Ridzon, a Senior Program Officer in the HIV Program at the Bill & Melinda Gates Foundation, focuses on HIV prevention. She currently holds clinical appointments in the Division of Infectious Diseases and the Department of Epidemiology at the University of Washington and in the Division of Infectious Diseases at Brown University, and serves on the editorial board of the *International Journal of Tuberculosis and Lung Disease.* Previously, Dr. Ridzon served as Assistant to the Director for HIV Prevention and Care in the Division of HIV/AIDS Prevention. She held the rank of Captain in the U.S. Public Health Service, where she received commendation, achievement and citation awards. While in Atlanta, she worked at the Grady Hospital HIV clinic and held an appointment in the Division of Infectious Diseases at Emory University. Dr. Ridzon received an MD from St. Louis University School of Medicine. She completed a residency in Internal Medicine at St. Louis University and a fellowship in Infectious Diseases at Brown University.

Dr. David S. Roos is the E. Otis Kendall Professor of Biology at the University of Pennsylvania, and Founding Director of the University of Pennsylvania Genomics Institute. He earned his undergraduate degree at Harvard College, a Ph.D. at The Rockefeller University, and joined the University of Pennsylvania in 1989 after a post-doctoral stint at Stanford University. Dr. Roos' research integrates diverse disciplines, ranging from molecular genetics and cell biology, to biochemistry and pharmacology, to computer science and genomics, to immunology and international public health. Current interests focus on protozoan parasites, including *Toxoplasma* (a prominent congenital pathogen and opportunistic infection associated with AIDS), and *Plasmodium* (the causative agent of malaria). Dr. Roos has received numerous awards, including the Presidential Young Investigator Award from the National Science Foundation, the Burroughs Wellcome Scholar Award, the Ellison Medical Foundation Senior Scholar Award in Global Infectious Diseases, and a Merit Award from the National Institutes of Health. He has published ~175 research reports in leading scientific journals, and travels widely as a lecturer and consultant for the WHO and other organizations.

Dr. Harvey Rubin is Professor of Medicine at the University of Pennsylvania with secondary appointments as Professor in the Department of Microbiology, the Department of Biochemistry and Biophysics and Professor of Computer and Information Sciences at the University of Pennsylvania School of Engineering and Applied Sciences. His research in infectious diseases has been funded by the NIH, NSF, DARPA and the Global Alliance for TB Drug Discovery. In addition to his work on the basic biology of

disease, he has extended investigations to mathematical modeling of complex biological systems. His research has resulted in more than 80 peer-reviewed papers chapters or reviews. Dr. Rubin served on a number of national and international scientific review panels including the NIH, NSF, NASA Intelligent Systems Program, DARPA and the Medical Research Council, South Africa. He is a member of the United States National Science Advisory Board for Biosecurity and the Department of Defense/National Academy of Sciences Biological Cooperative Threat Reduction Program. Dr. Rubin is the founder and Director of the Institute for Strategic Threat Analysis and Response (ISTAR) at the University of Pennsylvania. The mission of ISTAR is global—addressing strategies and responses to intentional as well as unintentional threats.

Dr. Carol Hopkins Sibley is a Professor in the Department of Genome Sciences at the University of Washington in Seattle, where her early work focused on immunology. Nearly a decade ago, a sabbatical year spent at the Institute of Molecular Medicine in Oxford piqued her interest in antimalarial drug resistance—a focus of her research ever since. Her lab is currently investigating the molecular mechanisms of antimalarial drug resistance. An active member of the international research community, Dr. Sibley has held positions at Seattle Biomedical Research Institute, the Nuffield Department of Medicine, University of Oxford, UK and the Walter Reed Army Institute for Research and maintained close collaborations with the KEMRI/Wellcome Trust Research Laboratories in Nairobi and Kilifi, Kenya. Dr. Sibley is also the Scientific Director of the WorldWide Antimalarial Resistance Network, which is funded by the Bill & Melinda Gates Foundation, and serves on the Expert Scientific Advisory Board of the Medicines for Malaria Venture, as well as the Boards of the ACT Consortium and the Liverpool-Malawi Wellcome Trust Unit. Dr. Sibley's recent articles include 32 peer-reviewed publications on malaria, tuberculosis and drug resistance. She holds a BA and MS in Biology from the University of Rochester and a PhD in Biochemistry and Biophysics from the University of California, San Francisco.

Dr. Suniti Solomon is the Director of Y.R. Gaitonde Centre for AIDS Research and Education (YRG CARE). Since her team first detected HIV in 1986, she has been working in this field. In 1993, she founded YRG CARE, a nonprofit organization that offers HIV and sexuality education for adolescents and youth, voluntary counseling and testing services and outpatient and inpatient services for more than 15,000 persons living with HIV, and that has international reputation as a premier medical and behavioral research center. Dr. Solomon serves as a scientific member on several national committees and has published extensively on HIV epidemiology, prevention, care and support, biomedical research, research ethics and gender issues. She holds an MD from Madras University. She has trained in pathology in the United Kingdom and the United States. She received a Lifetime Achievement Award for her work with AIDS from the State Government's Medical University in December 2001 and a second Lifetime Achievement Award in 2005 from the Tamil Nadu State AIDS Control Society. She was also awarded honorary doctoral degree in 2006 from Brown University.

Dr. Walter Straus, MD, MPH, is Global Director for Scientific Affairs for Vaccines at Merck Research Laboratories. In this role, he works with domestic and international vaccine experts to support the development of novel vaccines and to ensure that there is robust scientific information to assure that licensed vaccines are most sensibly evaluated and utilized. During his 10+ years with Merck, Dr. Straus has also worked in prelicensure development and postlicensure assessment of preventive and therapeutic products in the areas of infectious diseases, oncology, gastroenterology and rheumatology. Dr. Straus is a former Epidemic Intelligence Service Officer (and staff member) of the Centers for Disease Control and Prevention, where he worked in the area of

antimicrobial resistance. He serves as a Technical Consultant to the Agency for Health Research and Quality's Center for Education and Research on Therapeutics at the University of Alabama and holds an adjunct appointment with the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania. Dr. Straus has been actively involved in Public Responsibility in Medicine and Research and is the first member of the Board of Directors who was elected from the private sector. He currently serves as Chairman of the Board. Dr. Straus is trained in history (Harvard, AB), medicine (MD., SUNY-Buffalo), internal medicine and public health (both at the Johns Hopkins University) and gastroenterology/hepatology (University of North Carolina).

Dr. Thelma E. Tupasi is the founder and president of the Manila-based Tropical Disease Foundation Inc., the principal recipient of projects supported by the Global Fund to Fight HIV/AIDS, TB and Malaria in the Philippines. An internationally respected expert in infectious diseases, Dr. Tupasi chairs the DOTS-PLUS committee of the Stop TB Partnership; serves as chairman for the National Infectious Disease Advisory Committee to the Department of Health; and is a director of the Global Alliance for TB Drug Development.

Saul Walker is a Senior Policy Advisor in the Policy and Research Division at the UK Department for International Development. He leads on DFID's policy development to support access to medicines in developing countries, including innovation policy, supporting an enabling international policy environment, strengthening health systems to support access to medicines and improving the evidence base for policy making. He was previously Executive Director for Global Public Policy at the International Partnership for Microbicides and a Senior Policy Advisor at the International AIDS Vaccines Initiative. He is a board member of the Alliance for Health Policy and Systems Research and a Trustee Director of NAM Publications, a community HIV information provider.

Dr. Nicholas White, OBE, DSc, MD, FRCP, FMed Sci, FRS, is Professor of Tropical Medicine at the Faculty of Tropical Medicine, Mahidol University and Oxford University, and is also a Consultant Physician at the John Radcliffe Hospital, Oxford, UK. He has lived in Thailand and worked in the Faculty of Tropical Medicine, Mahidol University since 1980. Dr. White chairs the Wellcome Trust Tropical Medicine Research Programmes in Southeast Asia. He also currently co-chairs the World Health Organization antimalarial treatment guidelines committee and the WHO Global Malaria Programme case management cluster. His principal research interests are malaria, particularly antimalarial drug resistance, the pathophysiology and treatment of malaria and other severe tropical infectious diseases (melioidosis, typhoid, pyogenic, tuberculous and fungal meningitis, dengue, viral encephalitis, pneumococcal infections, diphtheria and tetanus). Dr. White is currently on the Editorial or Advisory Boards of 11 scientific journals including *The Lancet*, *PLOS Medicine*, the *European Journal of Clinical Pharmacology and Antimicrobial Agents* and *Chemotherapy*. He has published more than 750 scientific papers and 35 book chapters.

Prashant Yadav is a Professor of Supply Chain Management at the MIT-Zaragoza International Logistics Program and a Research Affiliate at the MIT Center for Transportation and Logistics. His research explores the functioning of pharmaceutical supply chains using a combination of empirical, analytical and qualitative approaches. Mr. Yadav serves as a consultant and adviser in the area of pharmaceutical supply chains to the World Bank, World Health Organization, UK Department for International Development, Roll Back Malaria Partnership, Bill & Melinda Gates Foundation, Medicines for Malaria Venture and many other global health organizations. He is the author of numerous scientific publications and his work has been featured in prominent print and broadcast media. Before academia, Mr.

Yadav worked for many years in the area of pharmaceutical strategy, analytics and supply chain consulting.

Alexandra (Alix) Beith spends half of her professional time as an independent global public health consultant and the other half as a Senior Health Analyst with Broad Branch Associates. She has 12 years of experience in a number of technical areas, including rational drug use, tuberculosis and health policy and financing. She has a master's degree in Health Policy, Planning and Financing from the London School of Economics and the London School of Hygiene and Tropical Medicine. She is fluent in Spanish, French and English. She has been contributing to the Drug Resistance Working Group project since November 2007.

Appendix E

Individuals consulted

Paulson Amibor, World Health Organization
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Tenaw Andualem, Strengthening Pharmaceutical Systems
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Silvia Bertagnolio, World Health Organization
Nancy Birdsall, Center for Global Development
Steve Blount, Centers for Disease Control
Mohammed Bollahi, CNTS
Tom Bollyky, Center for Global Development
Anthony Boni, U.S. Agency for International Development
Anstice Brand, Centers for Disease Control
Robert Breiman, Centers for Disease Control
Bill Brieger, Johns Hopkins University
John Brownstein, HealthMap
Eric Buch, University of Pretoria and the New Partnership for Africa's Development
Barry Bunin, Collaborative Drug Discovery
Otto Cars, ReAct
Peter Cegielski, Centers for Disease Control
Xuanhao Chan, International Pharmaceutical Federation
Kennedy Chibwe, U.S. Pharmacopeia
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Sara Cordeiro, World Health Organization
Ann Cronin, Centers for Disease Control
Marius de Jong, Embassy of the Kingdom of the Netherlands
Jean-Francois de Lavison, Merieux Foundation
Tony Delamothe, British Medical Journal
Michael DeRenzo, U.S. Trade and Development Agency
Scott Dowell, Centers for Disease Control
Gerald Dziekan, World Health Organization
Benjamin Ellis, World Health Organization
Sylvia Ernst, Collaborative Drug Discovery
Dennis Falzon, World Health Organization
Gilles Bernard Forte, World Health Organization
Michele Forzely, Widener Law
Pierre Joseph Fouda, CIRCB
Clark Freifeld, HealthMap
Bernardus Gamter, World Health Organization
Hellen Gelband, Resources for the Future
Fiona Godlee, British Medical Journal
Karen Goraleski, Research America
Andy Gray, CAPRISA and University of KwaZulu-Natal
Felix Greaves, formerly, World Health Organization
Robert Guidos, Infectious Diseases Society of America
Andreas Hedinni, ReAct
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Jim Hickman, formerly, One World Health
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Pat Hogan, Pfizer
Hans Hogerzeil, World Health Organization
Kathy Holloway, World Health Organization
Hope Hurley, American Academy of Pediatrics
Mini Jacobs, Tamilnadu Dr. M.G.R. Medical University
Ernesto Jaramillo, World Health Organization
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Ramanan Laxminarayan, Resources for the Future
Stefano Lazzari, World Health Organization
Dominique Legros, World Health Organization
Carmelina Leite, World Health Organization
Stuart Levy, APUA

Mary Lisa Madell, U.S. Department of Health and Human Services
Margaret Mafe, Nigerian Institute of Medical Research
Chris Manz, Duke University
Linda Miller, GlaxoSmithKline
Maria Miralles, International Relief and Development
Dominique Monnet, European Centre for Diesease Prevention and Control
Jean-Jacques Monot, Global Forum for Health Research
Dominic Montagu, University of California, Berkeley
Hassan Mshinda, Costech
Catherine Mundy, Management Sciences for Health
Jennifer Murphy, U.S. Agency for International Development
Carl Nathan, Cornell Medical School
Rob Newman, World Health Organization
Tom O'Brien, WHONET
Eve Odete, Oxfam
Eva Ombaka, formerly, Ecumenical Pharmaceutical Network
Philip Onyebujoh, World Health Organization
O. Otubanyo, Unilag
Katie Petersen, iBridge
Kyle Peterson, FSG Social Impact Advisors
Stefan Peterson, Karolinska Institute
Marjorie Pollack, ProMED
Pilar Ramon-Pardo, Pan American Health Organization
Mario Raviglione, World Health Organization
Pascal Ringwald, World Health Organization
N. Robinson, Government of Canada
Dennis Ross-Degnan, Harvard Medicial School and Harvard Pilgrim Health Care
Nalin Rostogi, Institut Pasteur de Guadeloupe
Cathy Roth, World Health Organization
Robert Schafer, Stanford School of Medicine
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Gabriel Schmunis, formerly, Pan American Health Organization
Miriam Schneidman, World Bank
Jens Seeberg, Uniarhus
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Robert Staley, Partnership for Supply Chain Management
John Stelling, WHONET
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Marian Warsame, World Health Organization
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Diana Weil, World Health Organization
Charles Wetherill, Whitaker Group
Karin Weyer, World Health Organization
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Mary Woolley, Research! America
Tana Wuliji, independent consultant
Serge Xueref, Global Fund to Fight AIDS, Tuberculosis and Malaria
Kathleen Young, APUA
Matteo Zignol, World Health Organization

Appendix F

Drug resistance information sources

This list covers the major global (and to a lesser extent, regional) sources of drug resistance information. The resources listed—which include databases and networks—generally focus on scientific data, with some also covering population and systems drug use data.[i]

Databases

HIV/AIDS

- **Los Alamos HIV Resistance Mutation Database (Archived):** A searchable compilation of mutations in HIV genes that confer resistance to antiretroviral drugs. It was created and maintained by staff at the University of Pittsburgh and the Los Alamos National Laboratory, but folded at the end of 2008 reportedly because of lack of financing. See: http://resdb.lanl.gov/Resist_DB/.
- **Stanford University HIV Drug Resistance Database:** This public, curated database was designed to represent, store, and analyze data underlying HIV drug resistance, including correlations between genotypes and other data, such as treatment history or outcome. It is maintained by a team at the Stanford University Medical Center. See: http://hivdb.stanford.edu/.

Malaria

- **WorldWide Antimalarial Resistance Network (WWARN):** The WWARN is developing a Web-based open-access database that will incorporate, integrate, and assure quality of current data on clinical, molecular, in vitro, and pharmacological aspects of antimalarial drug efficacy and resistance. The global network is coordinated by the Seattle Biomedical Research Institute and the University of Washington, with databases designed by the University of Oxford and housed at the University of Cambridge. See: http://www.wwarn.org/.
- **WHO malaria database:** This database was developed by WHO to inform a 2006 report on drug resistance in *P. falciparum*. The report itself committed WHO to maintaining the database over the long term. However, it is unclear whether the database will be made available beyond WHO.
- **Institut Pasteur International Network:** Little information is available about this database, which appears to be managed by the Institut Pasteur facility in Cambodia. The Institut Pasteur network also runs a resistance surveillance program, which appears to cover several disease areas. See : http://www.pasteur-international.org/FSP/.

Tuberculosis

- **International TB Genotype Database:** This is a *Mycobacterium tuberculosis* molecular markers database, with only limited information on drug-resistance patterns and patient characteristics. The database is maintained by the TB and Mycobacteria Unit of the Institut Pasteur de Guadeloupe (a nonprofit). Data are owned by the relevant researchers, but are freely available for query via the website. See: http://www.pasteur-guadeloupe.fr:8081/SITVITDemo.
- **WHO/TDR TB Specimen and Strain Bank:** The specimen bank aims to support TB test development and evaluation, and contains specimens from patients investigated for TB across a diverse range of settings. The strain bank was developed primarily to support pharmaceutical R&D and includes approximately 216 strains donated by labs across the world, showing all possible patterns of resistance to four TB drugs.
- **Euro TB MDR-TB Project:** This project houses a database containing both genotypic and epidemiological data from MDR-TB cases across the European region. Data are generated by research institutes and also submitted by quality-assured

i. The information here was gleaned from relevant websites or from discussions with those maintaining the databases or networks in question. The websites were originally accessed between January and April 2008, and then again in April 2010 for rechecking. Any subsequent changes or additions are not reflected.

laboratories from at least 24 countries. See the MDR-TB surveillance tab at: http://www.eurotb.org.

Other antimicrobial resistance

- **ARInfoBank (Closed):** This WHO database was closed due to the low quality of data coming in from developing countries and a lack of financial and human resources. See: http://www.who.int/drugresistance/infosharing/en/.

Surveillance systems and networks

HIV/AIDS

- **The Global HIV Drug Resistance Surveillance Network (HIVResNet):** A global advisory network of HIV drug resistance experts, established and managed by WHO in collaboration with the International AIDS Society. It maintains a surveillance system to measure HIV drug resistance among treated and untreated patients, and to build related capacity. It is anticipated that data shared through HIVResNet will aid the development of effective global and national strategies for HIV treatment and the prevention of drug resistance. See: http://www.who.int/hiv/topics/drugresistance/hivresnet/en/.
- **WHO HIVDR Global Laboratory Network:** A network of laboratories designed to support HIVResNet.

Malaria

- **WorldWide Antimalarial Resistance Network (WWARN)**: See 'databases' above.
- **Regional Networks:** All these networks—which are operational and effective to varying extents, with several now absorbed by WWARN—aim to strengthen their regional information base on parasite drug sensitivity, to inform national malaria treatment policies. All were, or are still, managed by a small secretariat based in one country within the corresponding region. In a few cases, networks are linked to another program, for example RAVREDA and the USAID-funded Amazon Malaria Initiative.
  - **East African Network for Monitoring Antimalarial Treatment (EANMAT)**
  - **Horn of Africa Network for Monitoring Antimalarial Treatment (HANMAT)**
  - **Mekong Network (MEKONG)**
  - **Red Amazonicaprala Vigilencia de la Resistencia a las Drogas Antimalariacas (RAVREDA)**. See: http://www.ops-oms.org/English/AD/DPC/CD/ravreda-ami.htm
  - **Réseau d'Afrique de l'Ouest pour le Traitement Antipaludique I (RAOTAP I)**
  - **Réseau d'Afrique de l'Ouest pour le Traitement Antipaludique II (RAOTAP II)**
  - **Réseau d'Afrique Centrale pour le Traitement Antipaludique (RACTAP)**
  - **Réseau de la Résistance aux Antipaludiques dans la Sous Region Ocean Indien (RERAOI)**
  - **South East African Combination Anti-malarial Therapy (SEACAT)**. See: http://www.malaria.org.za/Seacat/seacat.html

Tuberculosis

- **WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance:** This project supports countries to conduct TB drug-resistance surveys. Data are collected and reported regularly and are used to estimate the magnitude of TB drug resistance levels, monitor trends, evaluate the effectiveness of TB control programs, and inform national TB treatment policies. See: http://www.who.int/tb/challenges/mdr/surveillance/en/index.html .
- **The Supranational Laboratory Network (SRLN):** The network is now part of the broader **Global Laboratory Initiative (GLI)** structure and supports national reference labs to conduct

quality-assured drug susceptibility testing and provide data to the Global Project (above).

Other antimicrobial resistance

- **Asian Network for Surveillance of Resistant Pathogens (ANSORP):** Established to undertake surveillance studies on antimicrobial resistance across the Asian region, ANSORP is now one of the world's largest collaborative study groups working in this area, with 196 principal investigators across 135 centers in 14 countries. It is coordinated by the Samsung Medical Center in Seoul, South Korea. Current projects include those on community-acquired MRSA and hospital acquired infections, particularly pneumonia. The network also maintains the **Asian Bacterial Bank**, with more than 30,000 clinical isolates. See: http://www.ansorp.org/.
- **Latin American Antimicrobial Resistance Monitoring/Surveillance Network:** See box 4.1 of this report for more detail or: http://www.paho.org/english/ad/dpc/cd/antimicrob.htm.
- **European Antimicrobial Resistance Surveillance System (EARSS):** A publicly funded European network of national surveillance systems, EARSS provides reference data on antimicrobial resistance for public health purposes. An interactive database allows user-friendly display of selected results in various downloadable formats, such as tables, figures, and maps. EARSS is managed by the National Institute of Public Health and the Environment (RIVM) in The Netherlands. See: http://www.rivm.nl/earss/.
- **Global Advisory on Antibiotic Resistance Data Project (GAARD):** This is a global public-private partnership involving the world's largest independent surveillance systems tracking antimicrobial resistance, many of which are linked to major drug manufacturers. Through coordination of data collection and joint analyses, the project identifies emerging drug resistance trends for major infectious diseases. It is managed by the **Alliance for the Prudent Use of Antibiotics**, a U.S.-based nonprofit (with chapters in 60 countries—30 in the developing world). See: http://www.tufts.edu/med/apua/Miscellaneous/gaard.html.
- **International Collaboration on Gonococci (ICG):** This is a voluntary, informal collaboration aiming to provide timely information to inform treatment for gonococcal disease by monitoring the emergence and spread of antimicrobial resistance in *Neisseria gonorrhoeae*. ICG is coordinated by Professor John Tapsall at the **University of New South Wales** and supported by a Web-based networking facility (membership required to gain access) provided by the Canadian public health system. See: http://www.icgngo.org/.
- **Network on Antimicrobial Resistance in *Staphylococcus Aureus* (NARSA):** This is a network of clinical and basic scientists from academia, industry, and public health. It aims to support cross-fertilization of biological, medical, and epidemiological research directed toward understanding resistance and other characteristics among staphylococci. NARSA is managed by **Eurofins Medinet Inc.**, based in Virginia, USA. See: http://www.narsa.net/content/home.jsp.
- **Reservoirs of Antibiotic Resistance Network (ROAR):** This network facilitates the sharing of data and literature on commensal bacteria to improve understanding of their role in the spread of antimicrobial resistance. Network members include more than 300 scientists from various disciplines in over 30 countries, who contribute to and use the ROAR database and moderated listserv. ROAR is managed by **APUA** (see above). See:http://www.roarproject.org/ROAR/html/index.htm.
- **WHONET:** The WHONET system is managed by a small team at the Brigham and Women's Hospital in Boston, MA, which designed freely downloadable software for labs to capture data on drug resistance. Most data are used locally, to inform treatment and infection control strategies, but can also be used to facilitate surveillance activities and appropriate policy responses at local, national, or regional level. See: www.whonet.org and http://www.who.int/drugresistance/whonetsoftware/en/.

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Center for Global Development

In an increasingly interconnected world, drug resistance does not stop at a patient's bedside—it threatens global health. It has slowed gains against the fatal ravages of childhood dysentery and pneumonia, drastically increased the costs of fighting tuberculosis and malaria, and imperiled efforts to effectively treat people living with HIV/AIDS. Tens of millions of lives are at stake; quality of life for scores of millions more is under threat.

The conclusions of the Center for Global Development's Drug Resistance Working Group make clear the need for urgent action to address this growing crisis. While there is no simple solution, there are achievable steps, as are described in this report, which the health community, governments, donors, and the pharmaceutical industry can and must take to slow the spread of drug resistance. Retaining the drugs we have now, developing new drugs and other technology, and ensuring these resources continue to save lives in future generations must become a priority for global and national health organizations, both public and private.

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