

## Drug Resistance as a Global Health Policy Priority

By Rachel Nugent, Jessica Pickett and Emma Back

### Abstract

Drug resistance is a major impediment to the successful treatment of HIV/AIDS, tuberculosis, and malaria – the three diseases prioritized for urgent action in developing countries – as well as serious illnesses such as pneumonia, diarrhea and other common infections worldwide.

Resistance emerges in response to epidemiological, socio-economic, and behavioral conditions stemming from common breakdowns in health systems, which have become more acute with new infectious disease burdens and investments in treatment. As a result, the significant investments being made in drug research and development (R&D) and in improving health care delivery in developing countries could be undermined by an increasingly ineffective range of therapeutic options, while developed countries also face increased health threats from the spread of multi-drug resistant strains of diseases.

Multilateral organizations, donors in global public health, the pharmaceutical industry, developing country governments and health care providers all have an interest in reducing the development and spread of drug resistance, yet inadequate attention has been paid to this problem and the full range of ways to deal with drug resistance have not been deployed. Strikingly, in fact, major decisions at both international and domestic levels about the pace and intensity of expanded access to treatment for certain conditions, as well as approaches to investing in R&D for second- and third-line therapies, are being made with relatively little consideration of implications for the spread of drug resistance, or the means of preventing it. This concept paper serves as an introduction to the issue from a global policy perspective, presenting some important considerations for policymakers, and proposing a process of analysis and dialogue to further refine those considerations into recommendations for action. It is provided as a background document for the Center for Global Development's Drug Resistance Working Group.

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# **Drug Resistance as a Global Health Policy Priority**

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## **Introduction**

Drug resistance is a growing problem worldwide and is of particular concern in developing country settings. It is a major impediment to the successful treatment of HIV/AIDS, tuberculosis and malaria – the three diseases prioritized for urgent action in developing countries. It also limits treatment options for serious illnesses such as pneumonia and acute diarrhea, and for other common infections.

The resistance of pathogens to drugs is a naturally occurring biological phenomenon, but the process may be stimulated or accelerated in response to epidemiological, socio-economic and behavioral conditions, which may in turn stem from health system weaknesses. The challenge presented by these conditions has become more acute with the increasing burden of disease and greater resources dedicated to treatment. As a result, the significant investments being made in drug research and development (R&D) and in public health in developing countries could be undermined as therapies rapidly lose efficacy. Further, in an increasingly globalized world, all countries face increased health threats from the spread of multi-drug resistant pathogens, wherever they originate.

Multilateral organizations, donors in global public health, the pharmaceutical industry, developing country governments and health care providers all have an interest in reducing the development and spread of drug resistance. Yet there has been insufficient attention to the problem and the full range of possible solutions has not been deployed. Strikingly, in fact, major decisions are being made at both international and domestic levels about the pace and intensity of expanded access to treatment for certain conditions, and about approaches to investing in R&D for second- and third-line therapies, with relatively little consideration to the implications for the spread of drug resistance, or to its prevention. At a minimum, lessons from previous experience should be applied, particularly in relation to the development of appropriate policies when new drugs enter the market.

This paper serves as an introduction to the issue of drug resistance from a global policy perspective, presenting some important considerations for policymakers, and proposing a process of analysis and dialogue to further refine those considerations into recommendations for action. It is intended as an initial background document to support deliberations by the Center for Global Development's Drug Resistance Working Group.

## **Background**

The past 50 years have been a golden age for human dominance over microbes. Since the discovery of penicillin in the mid-20<sup>th</sup> century, antibiotics – and more recently antivirals (and antiretrovirals) – have been the mainstay of the public health arsenal deployed against communicable disease

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alongside vaccines. But over time, genetic mutations have occurred, rendering microbes less susceptible to these drugs, and resistant microbes are being passed from host to host.<sup>b</sup> As defined by the *Disease Control Priorities Project*, “*de novo* or acquired resistance results in the appearance of a resistant strain in a single patient. Subsequent transmission of such resistant strains from an infectious case to other persons leads to disease that is drug resistant from the outset, a phenomenon known as primary resistance.”<sup>1c</sup>

Although the evolution of resistance is a biological phenomenon, it is influenced by human behavior, including that of governments, physicians and patients, as well as global stakeholders such as donors, pharmaceutical companies and technical agencies. The use of drugs against pathogens creates more pressure for selection than would naturally occur, allowing resistant micro-organisms to dominate susceptible ones. Now, only decades after the discovery of penicillin, efforts to control infectious disease are faltering. Resistance to many existing drugs is widespread and insufficient new products are on the horizon. Without a renewed effort to prevent the emergence and spread of drug resistant disease strains, coupled with the development of new treatment options, we will lose the fight to improve global health.

### The Market Does Not Protect Drug Efficacy

Put in economic terms, drug efficacy is a scarce resource with specific traits that imply a serious potential for overuse or depletion; its non-exclusive and transboundary nature means that inappropriate drug use anywhere can have implications for patients everywhere. Further, individual decisions take account only of the benefits and costs of using a drug *to that individual*. This represents a market failure, where the price paid by patients and providers does not reflect the full social costs of the associated increase in drug resistance (in economic terms, a negative externality). Similarly, research-based pharmaceutical companies and generic manufacturers do not bear the full costs of the decreased effectiveness of a drug class, so lack an incentive to take externalities into account in the development, management, pricing and promotion of medicines (at least under the current patent terms).<sup>d</sup> The pricing and promotion of pharmaceutical products are also subject to negotiation with each national regulatory authority. This complex situation suggests that there is a need for policy intervention to encourage actions toward a level of drug resistance that is optimal for society as a whole.<sup>23</sup>

There is likewise a strong case for international coordination to ensure that treatment of disease within a single country or region does not jeopardize the ability to treat disease elsewhere by increasing drug resistance.<sup>4 e</sup> Like environmental pollution, resistant microbes do not respect

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<sup>b</sup> Drug-resistant microbes, like all infectious organisms, can spread via unsafe drinking water, unsanitary conditions, and poor infection control in hospitals and other health facilities.

<sup>c</sup> Note that the actual terminology tends to vary by disease community; for example, TB experts generally refer to “acquired resistance” rather than *de novo*, which is used more frequently among malariologists.

<sup>d</sup> Whether or not industry has an economic incentive to preserve the useful life of a given antimicrobial would depend on whether the length of the patent term would allow them to capture the increased returns on the asset, or if they are able to profit from subsequent life-cycle management options, such as high-dose or extended-release formulations as in domestic markets. (Power, E. “Impact of antibiotic restrictions: the pharmaceutical perspective.” *Clinical Microbiology and Infection* Volume 12 Issue s5 Page 25-34, August 2006.)

<sup>e</sup> In some cases, such as malaria, *de novo* resistance has been shown to originate in one part of the world before spreading to Africa, where it is now most prevalent – which demonstrates that to be effective any solution has to be global in scope, not just targeted at the poorest or most endemic areas.

national borders, and even the most stringent systems to ensure rational drug use in one area can be undermined by resistant strains of a disease migrating from elsewhere. In addition, in the context of the global pharmaceutical market, transnational relationships and mechanisms such as development assistance, regulatory and trade regimes influence the onset of and response to drug resistance. Greater attention is necessary to the institutional, social and economic conditions contributing to drug resistance and to the incentives each global health actor has to limit its emergence and spread. International collective action is necessary, with the full engagement and cooperation of national authorities, donors, technical agencies and the private sector.

The global community therefore has a crucial role to play in providing incentives for better resource management, coordinating surveillance and response, and supporting the development of appropriate national drug policies and regulatory systems. Finance and technical assistance is also needed to support prescriber and patient education, particularly when new therapies are introduced. And investment by donors and private sector is needed to facilitate necessary R&D. However, the global community has been slow to commit itself to all these roles and to face the tough trade-offs between responding to short-term needs and avoiding longer-term problems.

At the global level, the World Health Organization's efforts to educate and promote good practices are considerable, and the organization has a critical and unique role to play given its intergovernmental status and mandate. However, its financial resources are severely limited and member state commitment remains uneven.<sup>f</sup> There are other organizations working on drug resistance, many of them very competent, but they tend to focus on one or two aspects of the problem rather than tackling the agenda comprehensively. Without stronger co-ordination or a clear international agreement, it remains possible for individual nations and actors to free ride on others' efforts to protect what is in effect a "common property resource" – that of drug efficacy.

### The Burden of Drug Resistance Should be Equitably Distributed

Technically, of course, the emergence and spread of new resistant pathogens could be significantly reduced if new treatments were strictly rationed. While that is obviously undesirable, it illustrates the point that as developing country governments, donors and others strive to reduce morbidity and mortality by maximizing access to new therapies now, the unintended consequence is to accelerate the development of drug resistance that will impact on future generations.

This raises important ethical and philosophical questions about how costs and benefits should be weighted across nations and generations. Almost any discussion of interventions to address resistance implicitly incorporates a discount rate, balancing the health of current patients against future ones (or current economic costs against future savings). Behavior in favor of immediate and widespread treatment reveals a high implicit discount rate; thereby privileging today's patients over tomorrow's. Even a small difference in that calculation can have significant ramifications for the intergenerational tradeoffs. In this case, we are also dealing with significant uncertainty about whether and when new treatment options (or other health technologies) may become available, and these would alter any cost-benefit analysis.

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<sup>f</sup> WHO's global strategy on Antimicrobial Resistance (AMR) was written in 2001, and remains relevant, though its implementation has been patchy. Its goals have been reinforced by two World Health Assembly resolutions – one in 2005 on AMR and another in 2007 on rational use. As yet, however, there is little evidence that additional resources will flow to this important area of WHO's work.

Particularly in areas with a high communicable disease burden, public officials are torn between the need to protect long-term drug viability and achieving near-term improvements in health within existing resources. Moreover, their efforts to preserve the efficacy of drugs for the long-term may be jeopardized unless neighboring countries also take similar actions. This reinforces the point made above that no single nation or actor has the incentive or ability to act alone to achieve the desired social aims. But historical precedent indicates that in the face of a shared problem – for example, the threat of avian influenza – the global health community can collaborate to deliver an effective international response.

It is one thing to recognize a problem, and quite another to manage it. While there is a relative paucity of knowledge about “what works” at the global policy level when it comes to combating drug resistance, extensive literatures in environmental economics, international law and collective problem-solving can be drawn upon for lessons. On the management of common property resources, policy actions on global environmental issues – such as climate change and depletion of the ozone layer – may be instructive. Also promising are examples of policies that effectively incentivize individual decision-makers to consider the effect of their actions on others and of approaches towards valuing a scarce and diminishing resource – such as water or forests. Translating the success of these international agreements into the public health context may be difficult, though some examples can be found in the field of environmental health, such as the Stockholm Convention on Persistent Organic Pollutants (POPs) and the Rotterdam Convention (which promotes shared responsibility and collaboration in the trading of hazardous chemicals, through a set of legally binding Prior Informed Consent (PIC) procedures). There are limited examples of mechanisms promoting a shared responsibility to prevent global health crises, though the recently agreed Framework Convention on Tobacco Control (FCTC) may be a relevant case study.<sup>§</sup>

### Drug Resistance in Developing Countries

The drug resistance challenge is especially severe in developing countries, where the burden of infectious disease is greatest, the potential for transmission is exacerbated by poverty and conflict, and infected patients have limited access to quality healthcare. While the past decade has witnessed a sea change in the global health landscape, with billions of dollars in new funding dedicated to the delivery of critical medical technologies for the developing world, global and domestic supply chains are still struggling to catch up. One of the most urgent symptoms of overstretched health systems is the increasing emergence of resistance to the pharmacopeia available to treat AIDS, TB, malaria and other serious illnesses. With both the public and private sectors working to increase access to existing products and encourage the development of new ones, it has become more important than ever to sustain the effectiveness of the drugs we have and to ensure that the R&D pipeline is constantly refreshed to expand therapeutic options over the long-term. To achieve these goals, we must work to address factors influencing drug resistance in three key areas: developing country health systems, individual behaviors (particularly those of prescribers and patients), and science and technology.

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<sup>§</sup> The FCTC is the first international agreement in the public health field to be negotiated under the auspices of the WHO and has been hailed as “one of the most widely supported treaties in the history of the United Nations” by WHO Director-General, Dr Margaret Chan. See: <http://www.who.int/tobacco/framework/en/>. This Working Group will review lessons from international negotiations on tobacco control, and other international agreements and enforcement mechanisms, to ascertain whether and how they might inform collective action to protect drug efficacy.

### *Developing country health systems*

Serious but common breakdowns in health systems create the conditions for accelerated drug resistance with contributions all along the supply chain – from drug development and procurement to regulatory requirements right down to providers’ prescribing patterns. Those that most directly affect resistance arise from weak regulation, poor supply chain management, a lack of knowledge and training among providers, inadequate monitoring and control systems in hospitals and other care facilities, and insufficient human and other resources. Ultimately, these weaknesses affect patient access, drug affordability and compliance with treatment regimens – which are key factors in the prevention and containment of drug resistance.

In 2004, about \$550 billion worth of medicines were sold worldwide. Expenditure on medicines can account for as much as 40% of a country’s health budget.<sup>5</sup> In developing countries, medicines account for between 25% and 75% of all healthcare expenditures, though these costs are often met ‘out of pocket’ (i.e. paid for directly by the patient, rather than through state provision or insurance schemes).<sup>6</sup> Developing country markets for health commodities have grown to represent an increasing share of the global market by volume (though importantly not by value), often without the concomitant strengthening of the regulatory environment and supply chain practices needed to ensure rational drug selection and use.

### *Individual behaviors*

Other contributors to resistance relate to individual behaviors. The importance of patient behavior should not be underestimated – factors such as poor adherence or the overuse of antibiotics (particularly in the absence of a diagnosis) can speed the evolution of drug resistance. There are significant social and environmental factors that limit the capacity of patients to adhere to treatment, and incentives and enablers to eliminate barriers to adherence are not commonly used in developing countries (unlike in the US). Even the cost of transportation to the clinic, or lack of the food needed to take with medicines can pose a barrier to adherence. Conversely, making treatment centers accessible to patients, enhancing treatment through the provision of transportation costs or food supplements can all improve treatment completion rates and decrease the risk of resistance developing.<sup>h</sup> It is also important for health workers to talk to patients to understand their drug use patterns and to try to affect patient behavior, as patient education is currently very inadequate.

The behavior of those involved in drug selection is also critical. Challenges include misdiagnosis, poor prescription practices, sub-therapeutic dosage, and the distribution and sale of substandard drugs. There are few sanctions against poor drug selection and use, and there is scant attention given to conflicts of interest, such as those that may be faced by a prescriber who also dispenses medicines (often to generate additional income). Other provider decisions that influence patient behavior – and subsequently resistance – include unsympathetic treatment, health facilities that cannot ensure regular drug supplies or that are open only at times patients need to be at work, and requests by staff for supplements in cash or kind. These factors are long-standing, and many are relevant to

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<sup>h</sup> For example, conditions of economic disparity can be favorable for the development of drug resistance—even more so than broad-based poverty. A famous example is Lima, Peru, where in 1996 an MDR-TB epidemic was discovered in the barrios. Such environments are fertile for the development of drug resistance, because while the poorest often lack access to quality TB services, they can acquire medicines through the private sector or through the informal marketplace. Oftentimes individuals will sell off assets to purchase even a month’s supply of medicines, or purchase medicines intermittently as their finances allow. Resistance easily develops through such partial or incomplete treatment.

industrialized countries too, but the situation has become more acute with the increased burden presented by diseases such as HIV and TB and with the corresponding investments in treatment.

### *Effective and accessible technology*

Donor support – combined with changes in trade agreements, intellectual property regimes and industrial capacity – has increased the supply of quality-assured medicines internationally, but such medicines are not always available or affordable locally, particularly in poor and remote communities. One consequence is that substandard products, including deliberate fakes, are increasingly filling the gap in the market, and have taken a firm foothold in many countries.<sup>1</sup> Indeed, according to WHO, about a quarter of the drugs consumed in developing countries are counterfeits; and in some countries this rises to nearly 50% (although some question whether these statistics rely on an overly broad definition of ‘counterfeit’).<sup>7, 8</sup> Many (though not all) of these drugs offer limited or no therapeutic value to the sick patient. Those that contain sub-therapeutic levels of active ingredients may accelerate the evolution of resistant pathogens, in addition to reducing the likelihood of treatment success.<sup>9 j</sup>

The relationship between drug prices and drug resistance is ambiguous. Higher prices may reduce the number of people taking drugs unnecessarily, but it could alternatively lead to patients buying and taking incomplete doses, or using substandard substitutes, promoting the spread of resistance.<sup>10</sup> The latter scenarios are particularly likely in developing countries, where there is relatively weak oversight of the pharmaceutical sector, and perhaps even more so in middle-income countries like India, Thailand, South Africa and the former Soviet Union, where incomes are high enough and health systems strong enough to facilitate access to medicines – but not enough to do so in a regulated and reliable manner. So while part of the solution is reducing the misuse or overuse of medicines, another component is actually *increasing* access to medicines (with support through associated health systems strengthening) to ensure that patients complete appropriate treatment.<sup>11</sup>

A further solution may be found in improved drug resistance surveillance. This entails both assessing and reporting the extent of drug resistance and monitoring drug use patterns. Some support is given to developing countries in these areas on a disease-specific basis through WHO and global health partnerships such as Stop TB and Roll Back Malaria, but coverage is very limited. In general, however, there is limited collection and sharing of information about the extent and type of drug resistance across developing country settings. There is no global database on antimicrobial resistance (AMR) for example. For malaria specifically, some recent progress has been made. A number of regional disease surveillance networks have been established (such as EANMAT for East Africa and RAOTAP I and II for West Africa) and these facilitate information sharing about

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<sup>i</sup> Drugs may be substandard because they contain insufficient active ingredients (sometimes due to poor manufacturing, and sometimes because they are deliberate fakes) or because they have degraded due to inappropriate packaging, transportation or storage. And even quality-assured products might not have been designed for resource-constrained settings. It is important to note, however, that some definitions of ‘fake’ or ‘counterfeit’ include effective products that are incorrectly labeled or circumvent intellectual property laws. Better data on the true nature and extent of counterfeiting is needed to properly address the problem in all its forms, including insofar as it contributes to drug resistance. This is something that must be addressed by national drug regulatory authorities with support from the international community – it is not an issue that will be explicitly researched or addressed by this CGD Working Group.

<sup>j</sup> The influence of the level of active ingredient on the evolution of resistant strains depends on a number of factors including the replication rate of the virus, bacterium or parasite in question, the antimicrobial agent concerned, and patient biology (including rates of drug absorption and other pharmacokinetic factors).

antimalarial drug resistance and drug use. Plans are now in place to establish a World Antimalarial Resistance Network (WARN), which “will be a web-based global antimalarial drug resistance database that is accessible to all users. This comprehensive efficacy and resistance database will provide malaria control managers, surveillance programs and policymakers with up-to-date evidence of temporal and geographic trends in antimalarial drug resistance at the global scale and in real time.” Once established, WARN could greatly enhance efforts to successfully treat malaria, provided of course that the newly available evidence appropriately affects policy and practice.

In addition, the use of drug susceptibility testing (DST) in the clinical context may be of particular value.<sup>k</sup> Where patients are prescribed therapies to which they do not respond, this frequently results in poor outcomes for them and contributes further to the evolution of drug resistant strains. Testing patients before selecting their therapy – or immediately thereafter if treatment must be started urgently – can help avoid such outcomes. However, the infrastructure to support such testing is limited in many developing countries. There is a need for greater investment in laboratories and associated human resources, and in improving surveillance networks and reporting systems. Such activities would build on recently enhanced efforts to expand laboratory capacity, for example in the TB field. In addition, there are new tools available for the rapid diagnosis of MDR-TB, which offer a significant opportunity to restrict the spread of MDR-TB if they are used properly.

In some therapeutic areas, the range of treatment options is very limited. This is not only due to the access constraints highlighted above, but to the limited extent of communicable disease research and product development. A recent increase in investment and co-ordination – including through public-private partnerships such as the Global Alliance for TB Drug Development, the Medicines for Malaria Venture (MMV) and the Drugs for Neglected Diseases Initiative (DNDi) – is helping to expand therapeutic options, but this is clearly one area that would benefit from enhanced and sustained resource flows. Equally important – and perhaps more neglected – are diagnostic technologies (which aid rational drug selection) and preventive technologies such as vaccines (which limit dependence on drugs). There are several excellent initiatives in these fields, such as the Foundation for Innovative New Diagnostics (FIND), but they may require greater investment and supplementation to facilitate developing country access to new technologies over the near term.<sup>l</sup>

### The Costs of Drug Resistance

The availability and price of drugs in developing countries are influenced by the types and degrees of risk borne by manufacturers, donors, local wholesalers, pharmacists and other stakeholders – and this, in turn, affects the incentives for each actor to work to mitigate drug resistance. In general, for most actors, the rewards of immediate access (e.g. profit for the manufacturer, wholesaler, prescriber and/or dispenser; well-being for the patient) are deemed to outweigh the risks from a longer-term loss of drug efficacy.

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<sup>k</sup> “Susceptibility tests determine a microbe's vulnerability to antimicrobial drugs by exposing a standardized concentration of organism to specific concentrations of antimicrobial drugs. Susceptibility testing can be performed on bacteria, fungi, and viruses. For some organisms, results obtained with one drug predict results with similar drugs... Susceptibility testing occurs in vitro and may not account for many in vivo factors (e.g. pharmacodynamics and pharmacokinetics, site-specific drug concentrations, host immune status, site-specific host defenses) that influence treatment success... Testing can also determine the effect of combining different antimicrobials (synergy testing).” (The Merck Manuals online medical library: <http://www.merck.com/mmpe/sec14/ch168/ch168d.html>)

<sup>l</sup> The Working Group will examine these fields and will try to identify the areas where increased investment by global health actors would generate greatest return.

The ultimate public health costs of improper treatment far exceed those to the national budget or to individual patients. Inappropriate distribution and use of drugs can permit resistant strains to flourish, ultimately leading to therapeutic failure, greater medical costs, and extended and sometimes futile efforts to cure patients of what should be easily treatable diseases. The direct economic costs of drug resistance are the expenses incurred in longer medical treatment, the costs of developing and introducing replacement drugs for those that no longer work, the higher cost of new-to-market drugs, and additional screening and diagnostic expenditure to prevent the spread of resistant strains. In the US, for example, it costs several thousand dollars extra to treat an infection that is resistant to common antimicrobials; hospital-acquired infections alone are estimated to cost \$17-\$29 billion per year.<sup>12</sup> The indirect costs of drug resistance are harder to calculate, but include those arising from increased rates of patient morbidity and mortality and from the costly risk-reduction efforts required to limit the spread of resistant pathogens.<sup>m</sup>

From the perspective of funding agencies – who invest significant resources in the development and supply of essential medical technologies for use in developing countries – resistance to antimalarials, ARVs, TB drugs and other antibiotics should raise serious concerns. As resistance emerges and spreads, donors will see a diminishing return on their past investments, and they will likely be under pressure to invest yet larger amounts in the development of new products and in services to deliver them. Further, by providing financing and technical advice donors bear a very real responsibility to consider the unintended consequences of increased access to new therapies and to collaborate in the design of mechanisms to avert or deal with them.

### **Case Studies: Perspectives by Disease**

The risk of drug resistance arises from the presence of factors that vary by product and context. Risk factors are therefore arranged in different constellations for any given product depending on the state of the market.<sup>n</sup> Clearly, for each of the three priority diseases – HIV/AIDS, TB and malaria – both the drivers of drug resistance and the response to it will differ. Risk conditions affecting major microbial diseases, such as shigella, pneumonia and cholera, vary as well. As donors work to expand the availability of treatments for a range of other neglected and emerging diseases – from trypanosomiasis to avian influenza – resistance may develop to those treatments too, unless appropriate precautions are taken from the outset.<sup>o</sup> The following section briefly characterizes the challenges presented by science and drug technology issues, health system constraints and individual behavior for HIV/AIDS, TB, malaria and other microbial infections. The Working Group has commissioned a more extensive literature review and a paper characterizing the drug resistance challenge faced by those working to tackle these four disease areas.

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<sup>m</sup> To date, very little data is available on the true economic magnitude of the problem, though, and several experts have called for additional research on this front. (Laxminarayan, R. et al. “Drug Resistance” in *Disease Control Priorities in Developing Countries*, 2006; and Smith, R. and Coast, J. “Antimicrobial Drug resistance” in *Global Public Goods for Health: a health economic and public health perspective*, 2003.) The Drug Resistance Working Group will carry out a limited economic analysis of global drug resistance.

<sup>n</sup> The range of risk factors and how they affect classes of drugs within and across diseases will be a primary focus of new analytical work, commissioned by CGD for the Drug Resistance Working Group, with the objective of identifying key commonalities and differences that imply specific policy approaches.

<sup>o</sup> Such precautions would vary depending on the disease in question, but might entail observed therapy, use of combination therapies, drug susceptibility testing, and enhanced patient and provider education, for example.

## HIV/AIDS

By December 2006, it was estimated that 1.8 - 2.2 million people living with HIV/AIDS were receiving treatment in low- and middle-income countries.<sup>13</sup> Donor funding for HIV/AIDS has skyrocketed in the last decade from US\$ 300 million in 1996 to US\$ 8.9 billion in 2006, and there has been a five-fold increase in the number of patients receiving treatment since 2003 alone.<sup>14</sup> New organizations have sprung up at every level to develop, purchase, deliver and advocate for antiretroviral therapy (ART), and as a result the world has seen unprecedented levels of access to these otherwise prohibitively expensive products. Unfortunately, not all ARVs are used appropriately, and poor patient adherence contributes to the development of acquired resistance in infected individuals over time.

There is considerable evidence of ART resistance in industrialized countries. For example, it is estimated that the likelihood of accumulating resistance mutations within 6 years of commencing therapy is around 27%.<sup>15</sup> A recent US-based study has raised concerns that the prevalence of primary drug resistance may also be increasing over time.<sup>16</sup> This study found the primary resistance rate to be higher than in previous studies: 25% of treatment naïve individuals carried a strain resistant to at least one class of antiretrovirals vs. 8-20% seen in previous studies. Consequently, the authors recommended that all patients initiating treatment be tested for resistance (and not only those whose infection was known or suspected of taking place within the previous year as per current International AIDS Society (IAS) guidelines). Multi-drug resistant HIV has also been reported, most notably in 2005 in New York City, where one patient was infected with a strain that was both dual-tropic (able to use both CCR5 and CXCR4 co-receptors) and resistant to 3 major classes of antiretroviral medications.<sup>17,18</sup> This provoked a public health scare, with health authorities voicing concerns that a “super resistant strain” was emerging.<sup>p</sup>

Despite the relatively recent introduction of ART in many developing countries, some limited and patchy data on the levels of ARV resistance are available. Recent research suggests that ARV resistance patterns among treatment naïve populations worldwide seem to reflect geographic trends in ARV use. WATCH, a worldwide surveillance program,<sup>q</sup> found the rate of resistance (to any ART drug) among treatment naïve individuals to be 5.5% in Africa, 7.4% in East Asia, 5.7% in Southeast Asia, and 6.4% in Latin America, lower than in North America (11.4%) and Europe (10.6%).<sup>19</sup> Another study in the Cote d'Ivoire reported acquired HIV-1 ARV resistance prevalence levels of ~6-8%.<sup>20, 21</sup> However, these statistics are relatively hard to come by, as many information gaps still exist. One contributing factor to the murkiness of the data is the poor state of viral load diagnostic use in developing countries. Viral load monitoring would make a significant difference in efforts to identify and monitor emerging resistance, and would also help health workers to better assess adherence in the initial years after a patient commences ART.

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<sup>p</sup> For example, in February 2007, four men in Seattle who had not previously been on ART were found carrying a strain of HIV resistant to at least 2 classes of antiretroviral drugs, with partial resistance to a third class. (King, W. “Health officials warn of new HIV threat found in King County,” *Seattle Times*. February 2, 2007; and Paulson, T. “Four local men found to have drug-resistant strain of HIV,” *Seattle Post-Intelligencer*. February 2, 2007).

<sup>q</sup> WATCH stands for World-wide Analysis of resistance Transmission over time of Chronically and acute infected HIV patients. “WATCH is a multi-center retrospective cross-sectional study in collaboration with the WHO, CDC, CATCH and many researchers all over the world. The aim is to collect and analyze the reverse transcriptase and protease sequences of HIV in patients that have never been exposed to antiretroviral drugs, in order to compute the prevalence of resistance transmission.” (<http://www.umcutrecht.nl/subsite/spread-programme/Projects/the-WATCH-study>)

Securing long-term patient adherence is a particular challenge in resource-poor settings. Key factors include ARV side effects, stigma, financial and opportunity costs, and even unintended consequences of other social programs (see box 1). In addition, treatment in many settings is disrupted by expired products or stockouts in the supply chain, primarily due to poor forecasting, but on occasion due to the forced withdrawal of substandard products, as in the case of the recent recall of Roche's antiretroviral Viracept following identification of some faulty batches.<sup>22</sup> † Whatever the reason, an interruption in a patient's ART can lead to death for the patient, in some cases fairly rapidly.

**Box 1: Patient Adherence and Perverse Incentives in South Africa**<sup>23</sup>

One disturbing phenomenon is that some South African AIDS patients appear to have discontinued their free ART in order to qualify for government-funded disability payments, access to which typically depends on having a low CD4 count. After a relatively short time, patients taking ARVs experience a significant rise in their CD4 counts, which has the effect of disqualifying them for the disability payment. So individuals are faced with the desperate choice between their long-term health and short-term financial needs – and there is anecdotal evidence that they are increasingly choosing the latter. Up to 30% of patients at one AIDS clinic have reportedly discontinued treatment for this reason. These and other such patients intend to resume treatment once they have been approved for payments. As it stands, this could have the effect of deepening the South African AIDS crisis by both lowering the treatment success rate and increasing drug resistance. No matter how well-intentioned, this aspect of the welfare system needs to be reevaluated in light of such a strong perverse incentive.

This may in turn contribute to drug resistance in the community, and raises important tradeoffs between the individual patient's welfare (where resuming treatment in the presence of resistance can still have a marginal benefit) and that of society as a whole.. Unlike many other diseases, AIDS also affects people (at least to a limited extent) who can pay higher prices for the drugs in wealthy countries. Therefore, a strong market mechanism is already in place to incentivize the development of new therapies. As a consequence, a number of second-line ARVs are now being made available to approximately 4% of ART patients in developing countries (though many more will have failed first-line treatment) – albeit at around 10 times the cost.<sup>24</sup> More recently, concerns have been raised about the level of financing needed to provide these more expensive products to a growing proportion of patients. Indeed, the development of resistance has likely contributed to the push for compulsory licensing for first line ARVs by Brazil and Thailand, as their AIDS programming budgets – originally designed solely to provide generic first-line ART – are now seriously overburdened by more patients being moved to second-line treatment.<sup>5</sup>

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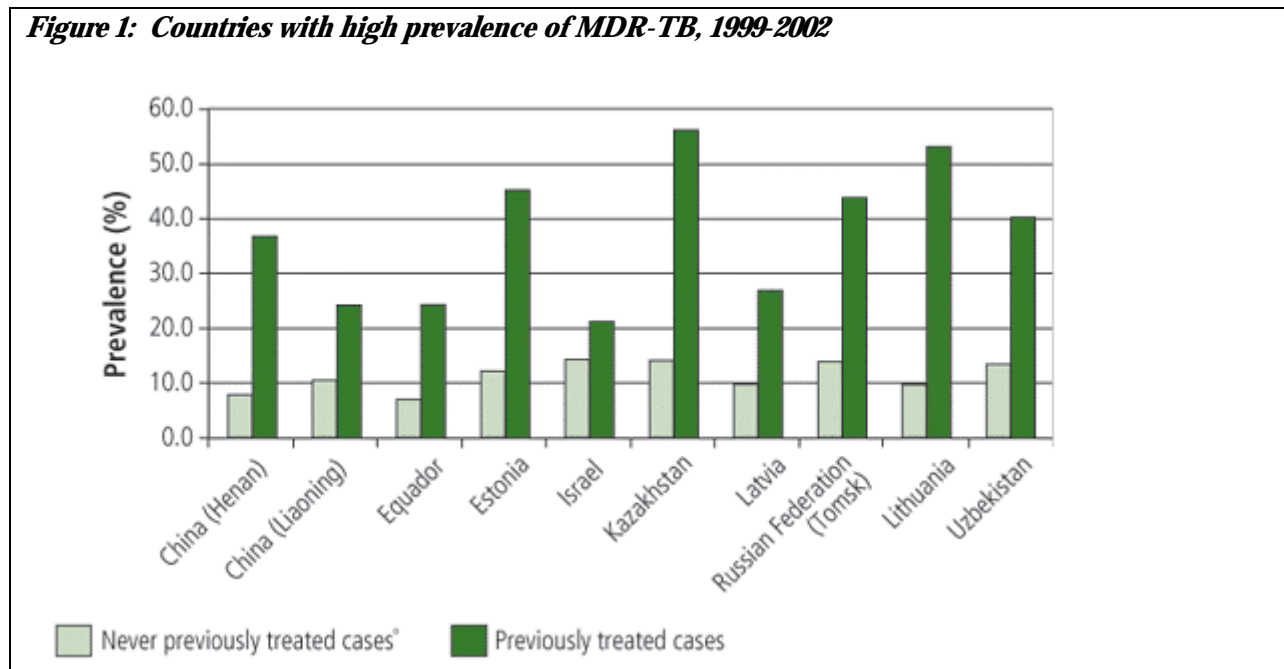
† Concern has also been expressed in the past about resistance among mothers to whom a single dose of nevirapine is administered during labor to prevent transmission of the virus to newborns; however, recent evidence suggests that delaying the start of a nevirapine-based ART by six months can prevent the development of drug resistance in HIV-positive women. (Lockman, S., et al. "Response to antiretroviral therapy after a single, peripartum dose of nevirapine." *New England Journal of Medicine*. January 2007)

<sup>5</sup> Under the current patent situation, for instance, Thailand could expect to spend up to \$500 million a year by 2020 if second-line therapy is adopted under its national AIDS program (compared to the current \$100 million in expenditures); by 2008 alone, second-line therapy would account for half of total ART spending. (Revenge, A., M. Over, E. Masaki, W. Peerapatanapokin, J. Gold, V. Tangcharoensathien, S. Thanprasertsuk. *The Economics of Effective AIDS Treatment: Evaluating Policy Options for Thailand*, World Bank: Washington, DC. August, 2006.)

## Tuberculosis

TB kills about 4,400 people *every day*, and is latent in more than one third of the world's population.<sup>25</sup> The current four-drug first-line regimen for TB has been in use since the 1960s and is only effective if patients complete a six to nine month course of treatment. To maximize patient adherence, these drugs are ideally administered under the direct observation of a healthcare worker or community member under the WHO-recommended DOTS strategy. Globally 61% of all smear positive patients were treated under DOTS programs in 2006, of which 85% had successful treatment outcomes. Similar rates are found for smear negative, although data are less comprehensive for extrapulmonary cases. Overall 5.1 million new cases of all forms of TB were notified and treated under DOTS out of the estimated 9.15 million cases in 2006.<sup>26</sup> Unfortunately, the associated burden on patients and providers alike has meant that up to many patients still do not complete treatment.<sup>27</sup> Moreover, the lingering use of non-DOTS approaches (such as the Russian Federation), combined with improper administration of the standard regimen, has led to approximately 424,000 cases of multi-drug resistant tuberculosis (MDR-TB<sup>†</sup>) globally each year.<sup>28</sup> The extent of resistance to each of the different TB drugs varies significantly between different settings, countries and regions, with the heaviest overall resistance burden borne by the Former Soviet Union. Indeed, in 2005, the WHO EURO region had the highest number of laboratory confirmed MDR-TB cases, accounting for more than half the global caseload.<sup>29</sup> Figure 1 provides an overview of MDR-TB levels among new and retreatment cases in high-burden countries.<sup>30</sup>

**Figure 1: Countries with high prevalence of MDR-TB, 1999-2002**



The rise of MDR-TB has major financial implications and entails greater country capacity to undertake the necessary treatment programs, which are several times more difficult than management of drug susceptible TB. In South Africa, a single course of treatment for MDR-TB costs roughly \$4300, compared to \$35 for a course of first-line therapy; in Peru, those figures are

<sup>†</sup> MDR-TB is defined as resistance to isoniazid (INH) and rifampicin (RIF)

estimated at \$8000 and \$267, respectively.<sup>31</sup> This provides a strong economic – as well as therapeutic – rationale for the use of expensive drug susceptibility testing (DST) where drug resistant TB is known to be present in the community (or even where it is not, when a patient fails to respond to treatment). However, the extent of DST varies a great deal within and between high-burden countries. The 2007 Global TB Report suggests that only 5 of the 22 high-burden countries undertake any kind of routine DST. The example of South Africa below highlights the potential consequences for the spread of drug resistant TB where DST is not routinely undertaken.

Of MDR-TB cases, 7% are cases of extensively drug resistant (XDR-TB).<sup>32, 33, u</sup> XDR-TB first captured the world stage in late 2006 with a deadly outbreak in South Africa, and again in mid-2007 with the misdiagnosis of US traveler Andrew Speaker. There are relatively few effective treatments for MDR-TB (and fewer still for XDR-TB), and those that do exist are of long duration and high toxicity. While the Global Alliance for TB Drug Development is working to develop new and improved treatment regimens, the prospects for a safer, affordable and effective treatment for MDR-TB, let alone XDR-TB, are very distant. Current efforts are largely focused on containing and treating resistant strains as well as preventing acquired resistance through the careful management of drug supply using the Green Light Committee. The success of this approach is dependent on improved diagnostics, as the widespread misdiagnosis of existing TB strains wastes time and money, and can even accelerate the development and spread of resistance (see Box 2). Current R&D efforts are being spearheaded by the Foundation for Innovative Diagnostics (FIND); similarly, recommendations on the use of TB diagnostics are being urgently updated by WHO in conjunction with the International Union Against TB and Lung Disease and others in the Global Project on Drug Resistance Surveillance.

**Box 2: The Lack of Drug Susceptibility Testing in South Africa’s DOTS+ Program<sup>34 35</sup>**

In 2001, South Africa adopted the DOTS+ strategy for identified cases of MDR-TB. Unfortunately, however, this did not include drug susceptibility testing (DST) for second-line therapies to ensure efficacy. As it turned out, a significant proportion of patients in KwaZulu-Natal were already resistant to at least one of the most common products, ethambutol, so patients were unintentionally treated with regimens that contained too few effective drugs – provoking a chain reaction that resulted not just in treatment failure, but in further selection of drug-resistant strains. In this manner, the adoption of DOTS+ likely *contributed* to the development of XDR-TB in the province by late 2006, when, in one well studied outbreak in Tugela Ferry, 52 out of 53 infected patients died within an average of 25 days following diagnosis. While poor or absent patient supervision (and the correspondingly low completion rates) were key ingredients to the outbreak, without DST and surveillance programs, the global community may have undermined rather than aided efforts to tackle drug resistance and lower the burden of disease.

It should be noted that finding solutions to the growing problem of drug resistance in TB is inherently more difficult due to the rise of TB/HIV co-infection. TB in HIV-positive patients is harder to diagnose and more likely to be disseminated. Patients with advanced HIV or AIDS are particularly susceptible to TB infection and are therefore also more likely to undergo successive

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<sup>u</sup> XDR-TB strains are resistant to any fluoroquinolone, and at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin), in addition to isoniazid and rifampicin. This is a revised definition of XDR-TB, on which the WHO Global Task Force on XDR-TB agreed in October 2006. However, some of the relevant literature is based on the previous definition of XDR-TB, under which the patients exhibited resistance to isoniazid and rifampicin and at least three out of six main classes of second-line drugs.

courses of treatment, which increases the likelihood of developing resistance to standard drug regimens if treatment is poorly managed. This can actually be aggravated by major ARV treatment programs, which have created a large concentration of immunosuppressed individuals. It is important, therefore, that any efforts to tackle drug resistance in TB fully consider the current and potential impacts of the HIV/AIDS epidemic and treatment programs.

## Malaria

In sub-Saharan Africa, malaria kills almost 1 million children under the age of five every year.<sup>36</sup> In response to the seriousness of this illness, antimalarial drugs are often administered presumptively to children with fever, resulting in significant over-treatment. The tendency towards overuse is further aggravated by the lack of cheap and convenient diagnostic tests. These factors accelerate the evolution of antimalarial drug resistance and complicate the management of other acute febrile illnesses. In one survey in Tanzania, for example, less than half of all children and adults admitted to hospital with suspected malaria actually had parasites in their bloodstream, but approximately half of these were still treated as such even in the presence of a negative hospital slide or rapid diagnostic test.<sup>37</sup> And whilst large quantities of antimalarials are administered without therapeutic benefit, many actual malaria cases go completely untreated, resulting in needless child deaths. Simple and accurate diagnostic tests are needed that can be administered in the community and are suitable for pediatric use (accompanied by patient and provider education about the appropriate response to a negative diagnosis). Indeed, there is an urgent need for improved diagnostics for childhood illness in general.

Historically, malaria (real or suspected) was treated with widely available and affordable drugs like chloroquine (CQ), accessed primarily through private sector distribution networks. However, the chemical properties and long half-life of the drug generated significant selection pressure on malaria parasites, with resistance emerging in *Plasmodium falciparum* by the end of the 1950s, first in South America and South East Asia and then spreading across Africa by the late 1970s. *P. Falciparum* CQ resistance levels in South America are now above 80%, approximately 50-60% in East and Central Africa, generally above 40% in the Eastern Mediterranean and Western Pacific, and approximately 10-30% in West and Southern Africa (see table below). Very little data exists for Central America.<sup>38</sup> CQ resistant strains of *Plasmodium Vivax* have also been reported in Brazil, Colombia, Guatemala, Guyana and Peru.

**Table 1: Global Levels of Drug-Resistant *P Falciparum***<sup>39</sup>

	Resistant to CQ	SP	Both CQ and SP	Mefloquine	Amodiaquine
<b>East Africa</b>	~50-60%	~10-20%			"Low"
<b>Central Africa</b>	~ 50-60%	~10%			"Low"
<b>Southern Africa</b>	~ 10-30%	~10-20%			
<b>West Africa</b>	~ 10-30%	~10%			
<b>Six African countries<sup>v</sup></b>			~3-13%		
<b>Eastern Mediterranean</b>	Above 40%	Below 20%			
<b>Western Pacific</b>	Above 40%	~20-40%		~10-20%	
<b>South East Asia</b>	~40%	Around 20%		Above 20%	
<b>South America</b>	Over 80%	Close to 20%			
<b>Central America</b>		~10%			

<sup>v</sup> Comoros, Eritrea, Rwanda, Sudan, Uganda and Zimbabwe

Despite this widespread resistance, there is still hope that CQ could reemerge as an effective treatment option. This might occur through the use of drug cycling: a strategy to reintroduce the treatment, in the hope that it would regain efficacy in a more naïve parasite population.<sup>40</sup> A recent study of CQ in Malawi achieved a 99% cure rate in 105 children taking the drug, more than 12 years after it was originally withdrawn (due to treatment failure rates of over 50%).<sup>41</sup> While this is the first time that a popular drug has regained effectiveness after a break in its use, drug cycling may hold promise for other drugs too.

Sulfadoxine–pyrimethamine (SP) was one of the first successors to CQ, but in many areas resistance emerged within 5 years of extensive use (although current levels of resistance to SP, and of resistance to amodiaquine (AQ), vary dramatically by country depending on historical treatment protocols).<sup>w</sup> Mefloquine resistance levels have been reported at 10-20% in the Western Pacific and above 20% in South East Asia.<sup>42</sup> Confirmed or suspected resistance to primaquine, mefloquine and quinine has been reported in South America.<sup>43</sup> More recently, artemisinin-based combination therapies (ACTs) have been heralded as the last and best hope in the fight against malaria, and in early 2004 WHO recommended their widespread adoption as first-line treatment.

While ACTs are the most effective product currently available, the costs of production, and hence the price, are significantly higher than traditional malaria treatments: \$1 or more, compared to just 10 cents for an average dose for CQ.<sup>x</sup> However, there has already been a surge in global concern about potential resistance among this class of drugs, particularly given the prevalence of sub-optimal products. These include: artemisinin (and its semi-synthetic derivatives artesunate and artemether) or other drugs with which it may be combined being used as monotherapies; poorly manufactured combination therapies; and counterfeit products. Scattered research has revealed between 20% and 90% of antimalarials in seven African countries to be of substandard quality,<sup>44</sup> as were 52% of artemisinin-based antimalarials in South East Asia. Many of these products contain low levels of active ingredient, which is of serious concern with respect to drug resistance – though one study found that up to 40% of antimalarials that were supposed to contain artesunate in fact contained no active ingredients at all.<sup>45</sup>

The international community has taken up the challenge to drive poor-quality malaria products out of the market. In 2006, WHO worked with producers of artemisinin monotherapies for malaria, resulting in 13 companies agreeing to voluntarily phase them out in order to slow the progression of drug resistance.<sup>46</sup> More recently, the World Bank has promoted the establishment of the Affordable Medicines Facility – Malaria (AMFm) to increase access and reduce resistance by pricing ACTs below monotherapies and other marginally effective products like CQ; its creation was endorsed by the Roll Back Malaria partnership board on November 29, 2007.<sup>47</sup> And several product development partnerships such as the Medicines for Malaria Venture are looking ahead to research the next line of treatment, if and when widespread resistance to ACTs does emerge. There are

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<sup>w</sup> SP is unique in that it also exerts pressure on the emergence of resistance in bacteria, such as pneumococcus and salmonella. (Feikin, DR et al. “Increased carriage of trimethoprim/sulfamethoxazole-resistant *Streptococcus pneumoniae* in Malawian children after treatment for malaria with sulfadoxine/pyrimethamine.” *Journal of Infectious Disease*. April 2000.)

<sup>x</sup> These costs are driven in part by the 14-month long production cycle, which depends on the agriculture production of a key component, artemisinin (from the Chinese wormwood tree), which is then combined with a second compound to hasten recovery and delay the onset of artemisinin-resistant parasites. This may change as synthetic artemisinin becomes available (see [http://blogs.cgdev.org/globalhealth/2006/04/scientific\\_brea.php](http://blogs.cgdev.org/globalhealth/2006/04/scientific_brea.php)).

renewed calls to eradicate the disease entirely,<sup>y</sup> and all of these measures – and others, including insecticide-treated bednets and residual household spraying to reduce transmission – will be necessary to curb resistance and achieve such an ambitious objective.

### Other Microbial Infections

In contrast to TB, in most other diseases patients are exposed to drug resistant microbes through primary transmission, or, in some cases, through horizontal acquisition of preselected resistance genes by infecting bacteria.<sup>48</sup> Common resistant pathogens include an array of enteric pathogens (such as salmonella, shigella and cholera), respiratory pathogens like *Streptococcus pneumoniae*, and others such as gonorrhoea. While there are relatively few studies of the magnitude of antibiotic resistance in developing countries, those that do exist combined with anecdotal evidence suggest a significant problem. For example, in more than 60% of hospitalizations related to salmonella, the infecting organisms are found to express multi-drug resistance; penicillin-resistance among gonococci exceeds 35% in sub-Saharan Africa and the Caribbean.<sup>49</sup>

The sensitivity of such pathogens is of particular concern in humanitarian settings, where disease outbreaks are frequent and spread rapidly amongst already weak and malnourished populations. Being able to treat patients empirically is vital, as diagnostic facilities and surveillance activities are sparse or non-existent. In addition, the full range of antimicrobials may not be available to emergency health workers. The growing problem of drug resistance in *Vibrio cholerae* and *Shigella dysenteriae* type I – both common causes of diarrheal disease outbreaks in conflict zones and refugee camps – is therefore of particular concern. For example, studies across several countries and populations have shown that *S dysenteriae* type I resistant to co-trimoxazole, ampicillin, tetracycline, chloramphenicol and (increasingly) nalidixic acid is spreading, and that resistance is also emerging to the more expensive and less available alternatives, ciprofloxacin and ceftriaxone.<sup>50</sup>

Alongside diarrheal disease, acute respiratory infections (ARIs) are a leading cause of child mortality. Bacterial ARIs kill more than 3 million children every year in developing countries, and *Streptococcus pneumoniae* is thought to be the cause of up to 70% of these infections. The same pathogen can also cause otitis media, bacteraemia and bacterial meningitis in children. Recent studies indicate that penicillin-susceptible strains of *S pneumoniae* have declined to between a half and two-thirds of the strains circulating in many countries, and to less than a quarter in some; this is additionally significant because strains resistant to penicillin are more likely to be resistant to other antibiotics as well. Indeed, *S pneumoniae* “clones” have been isolated that are resistant to penicillin, chloramphenicol, tetracycline and erythromycin and these clones are now thought to be widespread and predominant.<sup>51</sup>

As in developed countries, hospitals are a leading contributor to the spread of antimicrobial resistance. Evidence from South Africa, for example, suggests a 15% nosocomial infection rate.<sup>52, z</sup> Similarly, several studies of *E coli* and *S pneumoniae* indicate that resistance is more frequently

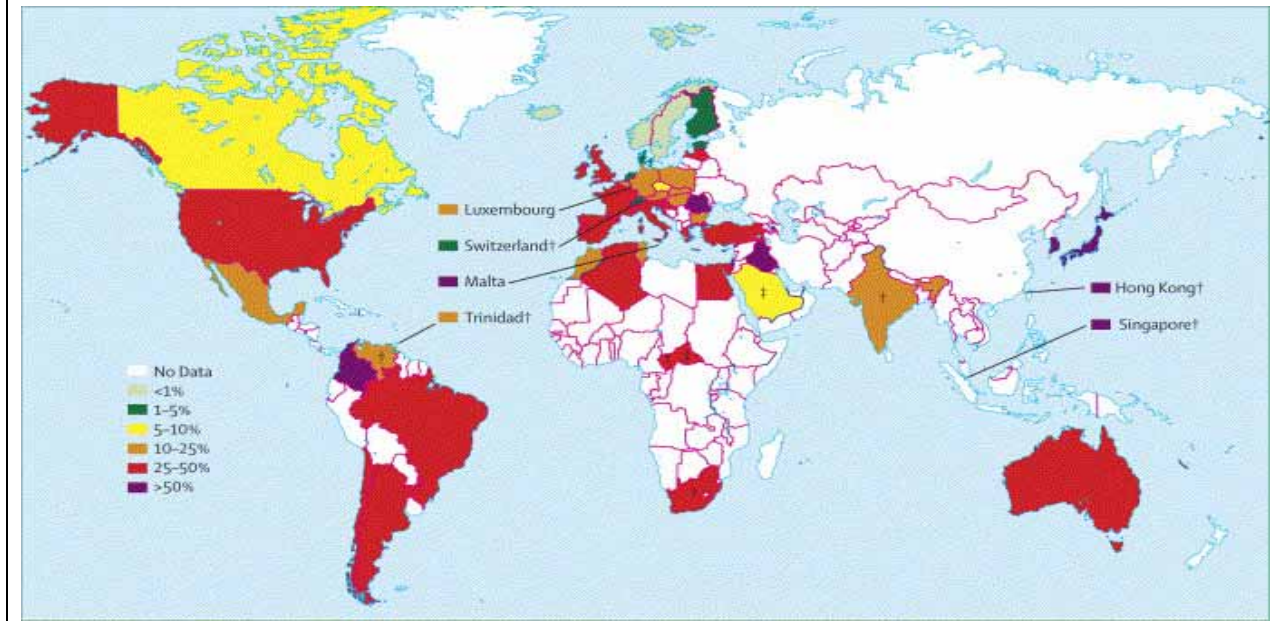
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<sup>y</sup> As proposed by Bill and Melinda Gates at the 2007 Malaria Forum in Seattle. Watch the original session through the Kaiser HealthCast ([http://www.kaisernet.org/health\\_cast/hcast\\_index.cfm?display=detail&hc=2288](http://www.kaisernet.org/health_cast/hcast_index.cfm?display=detail&hc=2288)) and see the Global Health Policy Blog ([http://blogs.cgdev.org/globalhealth/2007/10/malaria\\_eradication.php](http://blogs.cgdev.org/globalhealth/2007/10/malaria_eradication.php)) for a more detailed discussion.

<sup>z</sup> This issue may be addressed, to some extent, by the World Alliance for Patient Safety, which is prioritizing hospital hygiene and acquired infections and held its first awareness-raising workshop on patient safety in Africa in December 2007 (<http://www.who.int/patientsafety/about/en/index.html>).

encountered in urban areas than in rural settings, largely attributable to the greater accessibility of antimicrobials in cities.<sup>53</sup> One example of globalized AMR is methicillin-resistant *Staphylococcus aureus* (MRSA). This is a particular concern as a single genetic element confers resistance to the most commonly prescribed class of antimicrobials – the Beta-lactam antibiotics, which include penicillins, cephalosporins and carbapenems.<sup>54</sup> It has been estimated that, of approximately 2 billion individuals carrying *S aureus* globally, between 2 million and 53 million carry MRSA.<sup>55, 56</sup> Figure 2 presents a global snapshot of MRSA prevalence.

**Figure 2: Worldwide prevalence of MRSA by country<sup>57</sup>**



### *Antibiotics and animal health*

A separate contributor to antibiotic resistance is the use of therapeutic and sub-therapeutic levels of antibiotics in agriculture. Sub-therapeutic use (i.e. to promote rapid growth) is particularly controversial. This practice has been widely prevalent in industrialized countries, although it has been banned in Europe as of January 1, 2006.<sup>58</sup> In the US, when the use of fluoroquinolones in poultry was found to have contributed to the significant growth in fluoroquinolone-resistant strains of *Campylobacter* in humans, efforts were made to ban their use in poultry. The ensuing legal process lasted five years, culminating in a ban effective from September 2005, and was considered a public health coup.<sup>59</sup> However, public health success stories of this type are not often documented. In addition, examples of collaboration between experts in animal and human health are somewhat limited – a recent and notable exception being the case of avian influenza. Recent evidence from Canada, the US and Europe suggests the problem is even more severe than previously acknowledged. For example, the Union of Concerned Scientists estimates that at least 70% of all antibiotics consumed in the US are fed to animals on factory farms, while a recent Centers for Disease Control and Prevention study suggested that more than 20% of human MRSA infections in the Netherlands derive from an animal strain.<sup>60</sup> This is an area of the knowledge-base on resistance where further investment may be required, particularly in relation to data collection and analysis in

developing country settings, where relatively little research on the impact of agricultural and veterinary drug use currently exists.<sup>aa</sup>

### **Moving Towards Solutions**

As resistance becomes an increasing problem across a range of infectious diseases, many groups have begun to tackle individual elements of the problem. For the reasons elaborated above, we propose looking at drug resistance with a macro lens: across countries and across diseases. We believe that certain aspects of the required response must cut across geographic and scientific barriers to identify the potential economies of scale and scope to be gained from a systemic approach, and to defy the ability of resistant microbes to exploit gaps in the arsenal of prevention and containment tools. A comprehensive plan to deal with drug resistance will recommend diverse but interdependent actions at local, national, regional and global levels – all of which are important to success. The plan must incorporate feasible and credible mechanisms for financing, building capacity and timely response within developing countries. It is evident that – at least initially – many of these needs must be met by the developed world; but it should also be evident that a plan to prevent and contain drug resistance only in rich countries is not a plan at all – it is at best a delay tactic. Implementation across the many dimensions of resistance, both temporal and spatial, is needed.

There are at least three areas of focus at the global level that should be included in a systemic approach to prevent and contain drug resistance: management of drug efficacy as a common property resource, information sources and systems, and the research and development of new technologies. Each of these is a global public good and will be undersupplied if left to the private market. While a more coordinated approach is needed, several initiatives are already underway in each of these areas:

- Management of Drug Efficacy: Some efforts are underway to alter conditions that have led to increased drug resistance. At the technical level, increased attention is being paid to the potential of cycling strategies and directly observed therapy, in addition to combination therapy. However, many of these efforts are small and scattered; to the extent that these strategies rely on reducing the selection pressure on pathogens, it is important that they are undertaken at the international level in a coordinated manner.<sup>61</sup> And international initiatives to date, such as the 2001 WHO Global Strategy for Containment of Antimicrobial Resistance (as well as the 2005 and 2007 WHA Resolutions re-affirming it),<sup>62</sup> are profoundly insufficient to tackle the problem and are as yet only partially resourced and implemented.<sup>63</sup> More opportunities exist to harness the collective interest in conserving the viability of current and future drugs. The challenge is to determine which set of institutional incentives and system of governance can maximize the value to society of those resources, while respecting corporate and individual exigencies. Trade-offs will certainly be necessary; e.g. between short and long-term revenue and profit goals for manufacturers, among various treatment alternatives for providers and patients, and in program priorities for donors. Making those trade-offs explicit and opportunities for self-regulation more attractive are the first stages of achieving more sustainable management of drug resistance. An example of growing donor awareness of the trade-offs is the recent increase in investment in the

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<sup>aa</sup> While CGD recognizes the critical importance of animal health as a potential driver resistance, the current information gaps render it unlikely that the Drug Resistance Working Group will issue evidence-based recommendations in this area, beyond calling for further research.

development and roll-out of new accessible diagnostic tools to facilitate more rational drug use.<sup>bb</sup> In that spirit, a potential incentive tool could be for national governments to provide positive public recognition (or some desirable prize) for providers that increase use of diagnostics and achieve more appropriate treatment of patients.

- Information Sources and Systems: Currently, resistance prevalence and trends are understudied and the baseline data for evaluating the magnitude of the problem and the success of potential interventions is insufficient. Surveillance is the focus of a number of existing initiatives, such as the Global HIV Drug Resistance Surveillance Network and the nascent World Antimalarial Resistance Network (WARN).<sup>64, 65</sup> However, information needs go well beyond simply noting when and where resistance occurs: information is needed from the top to the bottom of the product supply chain to encourage appropriate choices around R&D investments, drug distribution and testing, prescription patterns and the use of diagnostics and drugs in different settings. An example of how basic surveillance data could be put to better use is in developing strategies for cycling of drugs – a potentially promising tool, but of little use without greater knowledge of both resistance events and the available pharmacopeia.
- New R&D: Part of the solution to drug resistance lies in increased R&D for the next generation of treatments, and we are seeing significantly enhanced commitment to the pipeline of products for infectious diseases. With subsidies from public-private partnerships, several large companies and biotechnology firms are working on new drugs.<sup>cc</sup> For example, as second-line treatments for AIDS are becoming available in developing countries, pharmaceutical companies are at work developing the third line of treatment. Research on new malaria drug and vaccine candidates has never been more robust. The pipeline for new antibiotics contains candidates across most classes of drugs, although far more are at the pre-clinical stage than at the more advanced stages of development. Notwithstanding these efforts, the benefits of any successful drug discovery will be greatly diminished if the new product is introduced into an environment that still does not protect the effectiveness of the drug once in use. And if we accept for the sake of argument that scientific inquiry into new products for the same diseases is subject to the law of diminishing marginal returns, and that microbes that have selected for existing classes and actions of drugs are stronger than ever, then maximizing the lifetime of new products becomes an urgent priority. New R&D on diagnostics is every bit as important as drug R&D, and policy changes in this area will have a far more immediate impact. FIND is already working closely with industry and academic research centers – in addition to specialized agencies, civil society and donors – to develop new diagnostics for TB, malaria and trypanosomiasis. Substantial investment in R&D for preventive technologies, especially vaccines, is also core to this strategy as well as being of direct public health benefit.

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<sup>bb</sup> For example, the Stop TB Diagnostics Working Group and the Foundation for Innovative New Diagnostics (FIND) have been working with a range of industry and non-profit partners to develop new TB diagnostics, such as the patch test, which would give rapid results and are suitable for resource poor settings.

<sup>cc</sup> There are also many small biotech companies engaged in diagnostic research for malaria and TB – such as Upstream Biosciences Inc, Cellectis Ltd, and Nutra Pharma Corp – and some have already developed new products. Many larger pharmaceutical firms are also engaged in communicable disease research, particularly in relation to new treatments – examples include GSK's infectious disease research center in Tres Cantos, Spain; AstraZeneca's TB research facility in Bangalore, India; and anti-malarial product development by Novartis and Sanofi-Aventis (the latter having worked with DNDi to launch a new product for malaria, ASAQ, in March 2007).

These types of solutions are complicated, as the benefits to future generations must be balanced against present needs.<sup>dd</sup> But there may be creative ways to encourage different actors to conserve drug efficacy as a shared resource. One relevant strategy is the subsidy of ACTs for malaria (now known as AMFm – see above), which was proposed by an Institute of Medicine panel in 2004 as a means of engaging the private sector supply chains in the fight against monotherapies.<sup>66</sup> Other proposals focus on extending patent terms to motivate drug manufacturers to develop new products or maintain the effectiveness of existing ones; it has been suggested that these efforts could be further amplified by revising the current regulatory requirements.<sup>67, 68, 69</sup> There may also be gains to be found farther down the supply chain by closely regulating product distribution and use, as in the case of the Green Light Committee for TB, or in strengthening legal enforcement against counterfeits.<sup>70</sup>

None of these global actions – better information, strategic common property management, and new R&D – are sufficient to prevent and contain drug resistance. With ever greater attention and money devoted to getting drugs to people, it is time to carefully consider the set of rules and procedures that provides the infrastructure needed to support new drug introduction and scale-up of access. To date, most efforts to quantify and address resistance have been undertaken by individual actors, and often on a disease-by-disease or even product-by-product basis. But these individual efforts aren't enough to solve the collective action problem, and don't maximize the potential economies of scale and scope from institutional changes that could benefit multiple disease areas. Now, the global health community needs to come together to build on these existing activities and solve the underlying institutional problems and constraints *across* diseases to improve the health of patients today, tomorrow and twenty years down the line.

### Working Group Objective and Approach

The Center for Global Development's Drug Resistance Working Group seeks to motivate changes in the policies and practices of global actors that would reduce the drug resistance affecting high-burden diseases in developing countries through improvements in common property management, information flows and R&D investments. Beyond simply identifying priorities for intervention, the Working Group will also consider the set of incentives, governance capabilities and actions, and financing mechanisms that could plausibly move the world in the right direction. We believe that a *common solution framework* can be brought to bear based on the risk factors for resistance across treatments for major diseases, and we will therefore draw on examples and lessons from HIV/AIDS, malaria, TB and other key microbial infections. The goal is to move away from short-term discrete responses towards creative big picture solutions – and to identify immediate steps that move us in the direction of correcting underlying institutional weaknesses and misaligned incentives and have long-term impact across all diseases and products.

The Group will draw on the strength of its diverse composition to extend the problem-solving conversation around drug resistance into and among communities that all have an interest, but rarely have the opportunity to forge joint solutions. The process will be designed and managed to generate critical thinking about the institutional, social, and economic conditions contributing to drug

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<sup>dd</sup> Solutions are unlikely to include sidelining new products until they are the only option, although such access control provisions are already used in some European countries, including Denmark and the UK, and are being discussed at the US FDA. Under these proposals, new products might be approved only for limited use in order to "save" them for later. This is likely to have greatest relevance for chronic diseases, where health care practitioners are under less pressure to make rapid drug selection decisions.

resistance and specific policy actions and investments that could be undertaken at a global level to reduce it. Specifically, the Working Group will consider questions such as:

- 1) What are the true economic costs of drug resistance in developing countries (including the morbidity and mortality from disease, treatment costs, and the costs of introducing replacement therapies), and which assumptions and methodologies should be employed?
- 2) What are the factors influencing different types of drug resistance, and how do they vary geographically and by disease?
- 3) What information is routinely collected, by whom, for what purpose, and with whom is it shared? Where are the gaps in the current surveillance efforts, and are there opportunities for collaboration?
- 4) What are the cross-country linkages that contribute to the transmission of resistance, and how is this influenced by behavior at the country-level?
- 5) Are there specific drug resistance principles or standards for product development and delivery to which individual actors should be held accountable?
- 6) What modifications or innovations in risks and incentives mechanisms could prevent the onset of resistance or curb its transmission? Are there existing models of collective actions that could be employed? What are the specific initiatives that major public and private sector actors should take over the next five years to reduce the spread of drug resistance?

The main product of the Working Group will be a policy report identifying practical and feasible actions. The report will include recommendations for consideration by the global donor community and other key stakeholders in global health, outlining the responsibilities different global actors should bear, while pointing out opportunities and needs at the local, national, and intra-institutional levels. The findings will be disseminated to decision-makers in key development and funding organizations, as well as key private sector interests, through targeted briefings, events and outreach.

## **Annex I: Glossary of Terms**

### *Primary resistance*

Untreated individuals with drug-resistant microbial species. The drug-resistant microbe is spread from host to host by the normal infection mechanisms.

### *De novo resistance (microbe)*

A drug-sensitive microbial strain that becomes resistant via changes in the microbes' genetic material – by mutation of their endogenous DNA.

### *Acquired resistance (microbe)*

A drug-sensitive microbial strain that becomes resistant via changes in the microbes' genetic material – by mutation of their endogenous DNA or by incorporation of drug-resistance-conferring DNA from another microbe. This is known as horizontal gene transfer and can occur between related or unrelated species.

### *Acquired resistance (individual)*

The individual initially has a drug-sensitive microbe, which becomes resistant due to inadequate treatment or poor adherence to treatment protocols.

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