Abstract

Drug resistance is a global challenge, affecting multiple diseases and recognizing no borders. Resistance to the pharmacopeia available to treat AIDS, malaria, tuberculosis, and other bacterial infections is rising and threatens progress in global health. Up to 10% of treatment-naive HIV+ individuals in the industrialized world have been found to be infected by relatively fit strains of HIV with resistance to one or more antiretrovirals. To date, the virtually untreatable extensively-drug-resistant (XDR) strain of tuberculosis has been recorded in 45 countries. Resistance to antimalarials is a common concern and a major threat to recently-introduced artemisinin-combination therapy. In the cases of the malaria parasite and other common developing-country pathogens, such as Shigella and V. cholerae, drug-resistant strains have been linked to higher levels of infant mortality. Effective treatment of common developing country respiratory diseases, too, is challenged by the presence of resistant strains.

This paper characterizes the drug resistance problem in developing countries. It first presents an overview of the magnitude of resistance to drugs among organisms responsible for high burden diseases, such as malaria, tuberculosis and HIV/AIDS, along with Shigella and V. cholerae (as representatives of enteric pathogens) and Streptococcus pneumoniae (representing major respiratory pathogens). It then analyses key drivers of drug resistance by classifying them into three major categories: 1) health system drivers, 2) behavioral drivers and 3) drug and drug technology drivers, recognizing that these drivers overlap and interact with each other. This classification system is then used to draw out commonalities in drivers across diseases. The paper also highlights gaps in knowledge about resistance, and priority areas for further research and potential policy dialogue. Given that existing efforts to slow emergence and transmission of resistance are primarily disease-specific, the main conclusion is that much might be gained from a more systematic response to resistance efforts.
Mapping Factors that Drive Drug Resistance
(with a Focus on Resource-Limited Settings):
A First Step Towards Better Informed Policy

Alexandra Beith
July 2008

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Resistance).
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACT</td>
<td>artemisinin combination therapy (for malaria)</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>APUA</td>
<td>Alliance for Prudent Use of Antibiotics</td>
</tr>
<tr>
<td>ARI</td>
<td>acute respiratory infection</td>
</tr>
<tr>
<td>ART</td>
<td>antiretroviral therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>antiretroviral</td>
</tr>
<tr>
<td>CGD</td>
<td>Center for Global Development</td>
</tr>
<tr>
<td>CQ</td>
<td>chloroquine</td>
</tr>
<tr>
<td>EWI</td>
<td>early warning indicator</td>
</tr>
<tr>
<td>FDC</td>
<td>fixed-drug combination</td>
</tr>
<tr>
<td>GOI</td>
<td>Government of India</td>
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<tr>
<td>HAART</td>
<td>highly-active ART</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>IAS</td>
<td>International AIDS Society</td>
</tr>
<tr>
<td>ICDDR,B</td>
<td>International Center for Diarrheal Disease Research, Bangladesh</td>
</tr>
<tr>
<td>IPT</td>
<td>isoniazid preventative therapy</td>
</tr>
<tr>
<td>IUATLD</td>
<td>International Union against TB and Lung Diseases</td>
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<tr>
<td>MDR-TB</td>
<td>multi-drug resistant TB</td>
</tr>
<tr>
<td>NARMS</td>
<td>National Antimicrobial Resistance Monitoring System</td>
</tr>
<tr>
<td>NNRTI</td>
<td>non-nucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>NRTI</td>
<td>nucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>NTP</td>
<td>National TB Program</td>
</tr>
<tr>
<td>PI</td>
<td>protease inhibitor</td>
</tr>
<tr>
<td>PNSP</td>
<td>penicillin non-susceptible \textit{S. pneumoniae}</td>
</tr>
<tr>
<td>REACT</td>
<td>(Group working on “Action on Antibiotic Resistance”)</td>
</tr>
<tr>
<td>SP</td>
<td>sulfadoxine-pyrimethamine (an anti-malarial)</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>Trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>extensively drug-resistant TB</td>
</tr>
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</table>
Background

Drug resistance is an evolutionary phenomenon that is an unavoidable consequence of treating disease with drugs. Measures can be taken, however, to slow the development of resistance by monitoring where and how resistance occurs, identifying its key drivers, and implementing risk reduction strategies. This is particularly important in the current global context where a vast increase in financial resources is being devoted to global health – including drug discovery and development.

Over the past decade the expansion of resources and the technological advances have meant that much larger quantities of drugs (particularly for malaria and tuberculosis (TB) treatment and human immunodeficiency virus (HIV) therapy) are available in developing countries than ever before. As a result, many more individuals are receiving necessary treatment or therapy than just ten years ago. This very welcome event is accompanied by the terrible irony that increases in drug availability and use can promote drug resistance and render the same life-saving drugs ineffective.

It is critical that the global health community devote considerably greater attention to resistance especially while antiretroviral (ARV) treatment is further expanded, action plans for switching national malaria treatment policies to artemisinin-based combination therapies (ACTs) are developed and implemented, and TB programs grapple with whether and, if so, when to provide widespread isoniazid (INH) intermittent preventive therapy (IPT).

Resistance is not a problem limited to the “big three” of AIDS, TB and malaria. Resistance to common antibiotics affects other major developing country diseases that have not received dedicated increases in funding over the past decade. Examples include diarrheal and respiratory diseases caused by pathogens such as *Shigella* and *Vibrio cholerae* and *Streptococcus pneumoniae*, respectively. These diseases are major causes of childhood death, accounting, for example, for 53 percent of all child deaths in 2001 in Sub-Saharan Africa.¹

It is encouraging that many global efforts targeting reduce drug resistance exist. For example, the World Health Organization (WHO) and the International AIDS Society (IAS) have recently created the Global HIV Drug Surveillance Network⁶ and Stop TB has a working group dedicated to multi-drug resistant TB (MDRTB)⁷. Several of Roll Back Malaria’s key working groups address resistance. The WHO antimicrobial resistance initiative was created in 2001 and private, non-profit approaches, such as the International Network for the Rational Use of Drugs (INRUD⁸), the Alliance for Prudent Use of Antibiotics (APUA⁹) and REACT, (Action on Antibiotic Resistance)⁰ emphasize local-level research and interventions, such as patient and provider education, and also serve as advocacy vehicles. These efforts would almost certainly benefit from increased coordination across diseases in order to better inform global policy-making and translate the evidence across disease areas into joint, coordinated and effective action.

The central hypothesis of this paper is that many of the systemic, behavioral, drug-related and biological factors that drive development of drug resistance are known and are similar across disease areas. Therefore, it is feasible to develop a common solution framework that can alter the factors driving

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² http://www.stoptb.org/wg/dots_plus/default.asp?AM=MDR
³ http://www.inrud.org
⁴ http://www.tufts.edu/med/apua
⁵ http://www.reactgroup.org/
resistance to treatment for these major diseases. The Center for Global Development’s Drug Resistance Working Group \(^8\) aspires to contribute to such a framework.

For the purposes of this paper we have chosen to describe resistance among a carefully selected group of pathogens that contribute substantially to ill health in developing countries. In addition to the headline diseases of AIDS, malaria and TB, we include resistance to the drugs used to treat *Streptococcus pneumoniae* (as “representative” of acute respiratory infections (ARIs)), and treatments for *Vibrio cholerae\(^h\) and *Shigella* (as representative of the resistance experience of enteric diseases spread by the fecal-oral route). It is beyond the scope of this paper to address resistance among all pathogens by name and specific treatment, but much of what is said here to understand resistance drivers can be applied to other drug-resistant pathogens affecting both developed and developing countries, such as methicillin-resistant *Staphylococcus aureus* (MRSA).\(^j\)

This paper first outlines methods used and general findings from review of the literature. It then provides a brief overview of how resistance develops biologically by type of disease/pathogen, with the goal of highlighting biological commonalities and differences. The next section “sets the global scene,” identifying resistance levels by disease (and, when possible) by region, with the aim of identifying recent trends and geographical areas where high levels of resistance have been documented. The paper then turns to the key factors driving drug resistance that policy can influence: health system drivers, behavioral drivers and drug technology drivers. Discussion of commonalities and differences in the drivers by disease follows. The final section outlines priority issues which merit further research and policy dialogue and offers conclusions.

**Methods**

To inform this review, the author primarily used information and evidence from published studies but, to the extent possible, also consulted grey literature and information from ongoing relevant work. Input from members of the Center for Global Development’s Drug Resistance Working Group and a number of other key individuals (listed in the acknowledgements section at the beginning of this paper) was invaluable. PubMed was searched using a combination of the following key terms: “resistance,” “drug

\(^8\) The DRWG is focusing on the potential for solutions effected collectively or individually by organizations that operate at the global level. The Group draws 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. In doing so, members stimulate each other’s active commitment to address the problem, possibly through changes in funding, policies and program implementation. The main product of the Working Group will be a policy report identifying practical and feasible actions (anticipated in Spring 2009). The report will include recommendations for the global donor community, outlining the responsibilities different 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. To learn more, visit www.cgdev.org/Drug_Resistance

\(^h\) Antibiotics are not the recommended line of treatment for *V. cholera*, except in crisis circumstances, such as cholera outbreaks in displaced populations sited around stagnant water resources. We chose to include *V. cholera* in this paper to 1) point to a disease area where drugs are used inappropriately (in non-cholera outbreak settings) and 2) highlight the critical need for effective antibiotic availability during crisis situations, especially given the fact that the conditions that support cholera outbreaks are becoming more frequent, especially in Africa.

\(^i\) There are four species of *Shigella: dysenteriae, flexneri, boydii* and *sonnei; with dysenteriae and flexneri being the most common in developing countries. While this paper will primarily address *S. dysenteriae*, it will raise examples and include information from other species as appropriate. *Shigella* is included in the paper given the fact that it is a high contributor to the global disease burden, specifically resulting in high mortality levels, primarily among children.

\(^j\) While MRSA has received considerable media attention in the developed world, the same can certainly not be said for developing country concerns such as resistance among diarrheal disease pathogens or those causing acute respiratory infections.
resistance,” “antimicrobial resistance,” “factors contributing to,” “factors causing,” “HIV,” “ART,” “tuberculosis,” “malaria,” “Shigella,” “V. cholerae” and “S. pneumoniae.” In addition, the same terms were used on the Google search engine. The number of articles identified per search string is provided in Annex I.

General findings from review of the literature

The drug resistance literature is mostly disease-specific and, with a few notable exceptions, limited to country studies of levels of and trends in resistance. Analyses of interventions to slow resistance are also disease-specific and thus reach a smaller audience than that which could be achieved if they addressed resistance across diseases (see Box 1 below).

Within the disease-specific literature about resistance, there is variability in accessibility and completeness of the information. The TB resistance literature is quite organized thanks to the efforts of WHO/IUATLD’s global drug resistance project. Information about resistance to AIDS drugs is primarily from developed countries. This is expected to change with increased ART accessibility and as a result of the Global HIV Drug Surveillance Network initiative (discussed later in box 4). Analysis of resistance to malaria drugs is scattered across numerous journals. Global information about drug-resistant pneumonia is very thorough up until the end of the Alexander Project covering the period from 1998-2000. The resistance literature concerning both Shigella and V. Cholerae is narrowly country-specific, and includes no analysis of interventions to slow resistance.

Box 1: Evidence of poor coordination of resistance efforts

Startling evidence of the lack of communication across resistance communities is captured in a paper by the REX Consortium which examines the structure of the scientific community involved in modeling the evolution of resistance. This study analyzed a database of 187 resistance-specific articles published between 1977-2006, specifically looking at co-authorship and co-citation networks in order to determine the extent to which scientists modeling resistance evolution collaborate and share their knowledge. The analysis classified the available research into three main groups, two large and one small and all quite distinct.

The groups were:
• One led by agronomists and ecologists focusing on agricultural pests and diseases which uses a population genetics approach to model the evolution of resistance to insecticidal proteins, insecticides, herbicides, antihelminthic drugs and miticides
• Another led by medical scientists focusing on human microbial parasites and which mostly uses epidemiological models to study the evolution of resistance to antibiotic and antiviral drugs and
• A third, much smaller, group focused on antimalarial resistance and only poorly connected to the other two groups.

Clearly these communities would gain from increased collaboration, information exchange and experience-sharing. Indeed, the authors conclude with the concern that “the lack of exchange between the…communities might slow progress concerning resistance evolution which is currently a major issue for society…(and that they fear) that this historical, field-oriented division impedes the progress of research at a time when the development of new pesticides and drugs is a growing problem.”

k The Alexander Project was a surveillance study that studied the susceptibility of pathogens involved in common adult community-acquired respiratory tract infections to a variety of antimicrobial agents
The “how’s” of resistance development: a brief biological overview of commonalities and differences in resistance development across bacteria (M. tuberculosis and other), HIV and the malaria parasite

Definitions of “resistance” across diseases?

The biological modes of resistance differ between and among types of bacteria, viruses and parasites. Further complicating a common understanding is that the processes through which resistance arises also vary depending on the class and type of drug to which resistance is developed. Resistance can arise within an individual on drug treatment or, alternatively, an individual can be infected with an already-resistant strain of the bacteria, virus or parasite. This paper uses the terms “acquired”\(^1\),\(^2\) for contexts where resistance emerges within a given individual on treatment and “primary” to define when an individual becomes infected with an already-resistant strain. Primary resistance is clearly the more alarming as it occurs at the population level; however some drug resistance begins as acquired and eventually is transmitted across individuals. The section below describes modes of pathogen resistance development, first for HIV, then for bacteria (including M. tuberculosis), and finally, for the malaria parasite. Differences in how resistance emerges and is transmitted across disease is an important element in determining the most appropriate and potentially effective cross-disease interventions to reduce resistance.

Modes of viral resistance development: the case of HIV

HIV antiretroviral resistance development was an inevitable phenomenon given HIV’s high mutation rate, the fact that monotherapy was the only form of treatment for several years and the additional consideration that treatment is required for life\(^3\). Resistance generally accumulates via step-wise mutation, often leading to a less susceptible virus rather than one that is completely clinically resistant\(^4\).

More than 150 known mutations are associated with HIV drug resistance (HIVDR) and various mutation interactions (meaning the ability of one mutation to influence the presence/absence of another) have been found\(^5\). RNA viruses such as HIV do not ‘proof-read’ genes during replication and so generate resistant mutants more rapidly than DNA viruses which do proof-read\(^6\). The likelihood of accumulating resistance mutations within six years of commencing antiretroviral therapy (ART) is estimated to be around 27%\(^7\).

Viral resistance can develop against a particular mode of action or a specific class of drugs\(^8\); indeed, an example of the former, which leads to class cross-resistance, is the case of the Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) class of ART\(^8\). HIV mutations can decrease fitness\(^9\), but this tends to be short-term, with “compensatory” mutations allowing mutant strains to quickly recover their fitness\(^9\).

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\(^1\) Recognizing that “de novo” is the term more commonly used to refer to resistance development via acquired route in malaria parasites

\(^2\) This choice is representative of language used in the literature reviewed

\(^3\) “HIV gene mutations may be classified as primary or secondary. Primary mutations alter the binding of a drug to its target, resulting in increased amounts of medications necessary to inhibit the target enzyme. Secondary mutations increase the level of resistance by improving the fitness of the virus carrying the primary mutations. Often, secondary mutations have little or no effect on the level of resistance in the absence of primary mutations.” (Maglione M, Geotz M, Wang Z, Wagner G, Hilton L, Carter J, Tringale C, Newberry S, Shekelle P. Antiretroviral (ARV) Drug Resistance in the Developing World. Evidence Report/ Technology Assessment No. 156. (Prepared by the Southern California Evidence-based Practice Center, under Contract No. 290-02-0003). AHRQ Publication No. 07-E014. Rockville, MD: Agency for Healthcare Research and Quality. September 2007.)

\(^4\) A simplified definition of which is “the capability of an individual of certain genotype to reproduce”. For more detail, please see http://en.wikipedia.org/wiki/Fitness_(biology)
Additionally, less fit strains still appear capable of producing disease. While ART resistance development is primarily through the acquired route, primary transmission of resistance also occurs\(^9\).

**Modes of resistance development: among bacteria**

Bacterial resistance can emerge through mutation of the pathogen in the individual undergoing treatment\(^6\), which is usually the case for *M. tuberculosis*. Tuberculosis treatment is complex, usually requiring combinations of three or four drugs for two months, followed by two drugs for an additional four months. Treatment of latent TB is 6-9 months long. Monotherapy leads rapidly to resistance, by selection of spontaneous mutants. Even with combination therapy, resistance emerges when there is poor patient adherence, incorrect dosage by the physician or mal-absorption, all of which can result in sub-therapeutic drug levels.

Bacterial resistance can be acquired by the microbe vertically (i.e., from its parent) or, in some cases, horizontally from another organism or strain. Genetic material conferring resistance that is acquired horizontally can then be transmitted vertically, particularly if there is selective pressure from the drug in question. Horizontal transfer can be of genetic elements that confer resistance, as is the case for beta-lactam and macrolide-resistant *S. pneumoniae*. Acquired resistance to beta-lactams and macrolides in *S. pneumoniae* is rare, requiring occurrence of more than one mutation\(^10\)^\(^11\); rather resistance in a population arises primarily through transmission of drug-resistant clones\(^12\). *S. pneumoniae* resistance to sulfamethoxazole-trimethoprim on the other hand (and which is more common) is primarily acquired, resulting from a single mutation (which can occur at a number of locations in the genome)\(^13\).

Resistance in *Shigella* bacteria can arise via plasmid transfer and, like *V. cholerae*, occurs primarily through primary transmission rather than through an acquired route\(^4\). However both *V. cholerae* and *Shigella* can also acquire resistance horizontally from the gut flora (commensal bacteria that normally resides in the intestine) containing genetic material conferring resistance\(^14\). Bacteria such as *Shigella* or *V. cholerae* that can share genetic material horizontally (and therefore resistant genes) clearly differ from organisms that do not have this ability (*M. tuberculosis*, viruses and parasites).

**Modes of resistance development: malaria parasite**

Like HIV, resistance in malaria parasites arises through mutation of genetic material (mutations in or changes in the copy number of genes encoding or relating to the drug’s parasite target or influx/efflux pumps\(^15\)). However, unlike HIV, these mutations are rare and are thought to be independent of the anti-malarial used\(^16\). Indeed, *P. falciparum* resistance to chloroquine is (CQ) thought to have arisen no more than ten times over the past half-century\(^17\). Acquired resistance usually arises in low transmission

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\(^9\) However, while “one person may put many people at risk … the transmission frequency per unsafe act is extremely low. There is no evidence in the US, or any other surveillance system, of rapidly spreading resistant (or sensitive) HIV strains.” (http://www.who.int/hiv/drugresistance/HIVDRSurveillance2006.ppt)

\(^9\) Naturally-occurring random genetic mutations render antimicrobials ineffective through a number of mechanisms including: increasing destruction of the antimicrobial agent, reducing drug uptake, increasing drug excretion, altering the antimicrobial agent’s target so that it is no longer bound by the drug and activating an alternative metabolic pathway that by-passes the drug’s target (Department of Health United Kingdom. The path of least resistance: main report of the Standing Medical Advisory Committee, Sub-Group on Antimicrobial Resistance. London: Department of Health, 1998).

\(^4\) Although acquired resistance must have occurred at some initial point(s) to allow the resistant strain to emerge and subsequently be transmitted by the primary resistance mechanism at the population level

\(^8\) Cholera can be transmitted through person to person transmission or through fecally-contaminated water. Additionally, *V. cholerae* acquired from an infected patient, rather than through contaminated water, may be more virulent and more transmissible. (Merrell, D. S., S. M. Butler, F. Qadri, N. A. Dolganov, A. Alam, M. B. Cohen, S. B. Calderwood, G. K. Schoolnik, and A. Camilli. 2002. Host-induced epidemic spread of the cholera bacterium. *Nature* 417:642-5)
settings in people with lots of parasites (hyperparasitaemic) who for reasons of drug quality, inadequate dose, adherence, absorption or distribution kinetics, or vomiting have inadequate blood concentration levels of the drug\textsuperscript{18}. Resistance mostly occurs through primary transmission of drug-resistant parasites.

Resistance in \textit{P. falciparum} has emerged to all classes of antimalarials to date, except for the artemisinin-based combination therapies (ACTs)\textsuperscript{19}. Resistance in \textit{P. Vivax} (a parasite which causes less severe disease than \textit{P. falciparum} and generally does not result in death), has been less studied, although there are recent reports of CQ resistance emerging in Indonesia, Papau New Guinea and South America\textsuperscript{20}. SP-resistant \textit{P. Vivax} is more widespread\textsuperscript{21}.

Table 1 summarizes the most common mode of resistance development among the pathogens under review in this paper.

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{Disease} & \textbf{More common form of resistance occurrence} \\
\hline
HIV & Acquired \\
\hline
\textit{M. Tuberculosis} & Acquired, and then Primary \\
\hline
\textit{Shigella} & Primary \\
\hline
\textit{V. Cholerae} & Primary \\
\hline
\textit{S. Pneumonia} & Primary (in the case of beta-lactams and macrolides) \\
& Acquired (in the case of trimethoprim-sulfamethoxazole) \\
\hline
\textit{P. Falciparum and P. Vivax} & Primary \\
\hline
\end{tabular}
\caption{Most common mode of resistance development by pathogen}
\end{table}

\textbf{Magnitude of the problem: an overview of global drug resistance levels and, where possible, recent trends}

This section provides an overview of the available data on drug resistance across the six focus pathogens. In most cases, resistance data is scattered, a reflection of the fact that in few cases (and for these only over the past decade or two) has drug resistance monitoring data been collected systematically. Where possible, data are presented by geographical region or individual country. The little trend information found is also highlighted. Geographical areas where high-levels of resistance have been documented are highlighted in Table 10, at the end of this section.

\textit{HIV drug resistance: levels and trends}

Very little global level data on HIV drug resistance can be found. Scattered data from industrialized countries provides a snapshot of what is occurring and a few developing country papers support this. One recent overview found that antiretroviral resistance patterns among treatment naïve populations worldwide seem to reflect geographic trends in ARV use. It reported ART-resistance levels of 5.5\% in Africa, 7.4\% in East Asia, 5.7\% in Southeast Asia, and 6.4\% in Latin America, all lower than in North America (11.4\%) and Europe (10.6\%)\textsuperscript{22}. Higher resistance levels in industrialized countries reflect the longer period of use (see Table 2 below for a list of ARVs and year of introduction), with only monotherapy as the treatment when ART came into being\textsuperscript{23}.

In the past few years, developing countries have rolled out HAART and studies to date have shown relatively high adherence rates\textsuperscript{24}. If adherence remains high, all factors equal, acquired resistance levels may stay relatively low. While resistance to ART occurs primarily through the acquired route; up to 10\% of newly infected, treatment-naïve individuals in the industrialized world have been found to be infected by relatively fit, strains of HIV with resistance to one or more ARVs\textsuperscript{25}. Despite this, many modeling efforts have given weight to the argument that the prevalence of transmitted resistance will most likely
remain low (and below the WHO 5% surveillance threshold) for several years in most countries currently undergoing rapid ART scale-up\textsuperscript{26} and indeed, data collected to date support this argument\textsuperscript{27}.

Multi-drug resistant HIV has also been reported, most notably in 2005 in New York City, where one patient presented 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. More recently, in February 2007, when four treatment-naïve men in Seattle were found carrying a strain of HIV resistant to at least two classes of antiretroviral drugs, with partial resistance to a third class\textsuperscript{3}. These events have rung alarm bells, with health authorities voicing concerns that “super resistant HIV-strains” might be emerging.

Finally, mention should be made of HIV-2\textsuperscript{28}, which manifests itself primarily in West Africa. HIV-2 also causes AIDS yet has a lower transmission rate, results in lower plasma viral loads and causes slower disease progression than HIV-1. HIV-2 infected individuals do not usually present symptoms. Therefore, if HIV-1 guidelines are used as the reference, most HIV-2 positive individuals do not require ARV therapy. However, if therapy is indicated and initiated, options are limited as HIV-2 is naturally resistant to NNRTIs and fusion inhibitors.

<table>
<thead>
<tr>
<th>Table 2: ARVs and year introduced</th>
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<tbody>
<tr>
<td><strong>Nucleoside reverse-transcriptase inhibitors</strong></td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
</tr>
<tr>
<td>Didanosine (ddl)</td>
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<tr>
<td>Lamivudine (3TC)</td>
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<tr>
<td>Stavudine (d4T)</td>
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<td></td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
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<tr>
<td>Zalcitabine (ddC)</td>
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<tr>
<td>Zidovudine (AZT)</td>
</tr>
</tbody>
</table>

A recent review by Maglione et al\textsuperscript{29} found the following country-specific data on resistance by type of antiretroviral:

Asia:
- A Northern Indian study from 2004 (N=60) found that, at a minimum, 80% of treatment-naïve patients carried a ZDV-resistant strain\textsuperscript{30}
- A Southern Indian study (N=50) revealed that 14% of treatment-naïve patients carried strains resistant to NNRTIs, 6% carried strains resistant to NRTIs, and 20% carried strains resistant to PIs\textsuperscript{31}
- A 2003 Mumbai-based study (N=128) of treatment-naïve persons at an outpatient hospital ward found that only two carried strains resistant to NRTIs\textsuperscript{32}

\textsuperscript{1} King, W. “Health officials warn of new HIV threat found in King County,” \textit{Seattle Times}. February 2, 2007; and Paulson, T. “Four local men found to have drug-resistant strain of HIV,” \textit{Seattle Post-Intelligencer}. February 2, 2007
\textsuperscript{u} The concern has been raised however that some of these studies only looked at people failing therapy and are not population-based studies and therefore they might be biased to detecting resistance.
• Only three other Asian-based studies were identified through the review. None of these studies reported NNRTI resistance, while reported NRTI resistance levels were quite low, ranging from 4-7%. Primary resistance to PIs was also low, ranging from 2-3%.

Africa:
• The review identified 14 ARV resistance studies in sub-Saharan Africa. Rates of NNRTI resistance ranged from 1-7.7% and NRTI resistance rates from 0-8% (in some cases, resistance to both classes was identified at a given study site).

Americas:
• The review captured eight ARV-resistance-related studies in Latin America (none of which was from Central America). NNRTI resistance rates were low, ranging from 1-2%; NRTI resistance among the treatment-naïve ranged from 2-14%.
• In the United States, it was estimated that 50% of HIV-infected individuals who were receiving care for HIV infection had some levels of ART resistance. This high level of resistance is the culmination of poor adherence, mono- or dual therapy prior to the introduction of HAART and the relatively poor potency of early HAART regimens.

Additional resistance data (not included in the above-mentioned review) includes:
• A recent US-based study which raised concerns that the prevalence of primary drug resistance may be increasing over time. 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.

Europe:
• A 2005 study in the UK of primary resistance prevalence trends for the period 1996-2003, found marked increases for all ART drug classes, and absolute levels that are among the highest recorded to date. For the 2002-2003 period, absolute levels were 19.2% (to any antiretroviral), 12.4% (to nucleoside- or non-nucleoside reverse transcriptase inhibitors), 8.1% (to non nucleoside reverse transcriptase inhibitors) and 6.6% (to protease inhibitors). Recent research from the UK found emergence of strains of HIV resistant to all three classes of currently-available ARVs. This research also found that, following two years of treatment with three different classes of ARVs, at least 10% of patients presented with a strain that has gained resistance to at least one drug. Following six years of treatment, up to 27% of patients presented with a strain resistant to at least one drug.

Tuberculosis resistance levels: levels and trends

Table 3: Drugs used to treat TB and year introduced

<table>
<thead>
<tr>
<th>1st line anti-TB drugs</th>
<th>Year introduced/Year resistance first reported (when information available)</th>
<th>2nd line anti-TB drugs</th>
<th>Year introduced/ Year resistance first reported (when information available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>1952</td>
<td>Fluoroquinolones</td>
<td>1980s</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>1963/1976</td>
<td>Ethionamide</td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>1962</td>
<td>Cycloserine</td>
<td>1955</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>1954</td>
<td>Para-aminosalicylic acid</td>
<td>1949</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>1944</td>
<td>Capreomycin</td>
<td>1970s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kanamycin</td>
<td>1970s</td>
</tr>
</tbody>
</table>

\(^v\) However some of these studies only addressed individuals failing therapy; they are not population-based studies and therefore they might be biased towards detecting resistance (R. Ridzon, personal communication)
MDR-TB: Multi-drug resistant TB, or MDR-TB, is the name given to disease caused by *M. Tuberculosis* strains resistant to at least isoniazid (INH) and rifampin (RIF). A WHO/IUATLD February 2008 report\(^3\) capturing TB resistance data from 91,577 patients in 93 settings in 81 countries and two of China’s Special Administrative Regions (SARs) during 2002-2006 found the highest rates of drug-resistant TB to date. New MDR-TB cases are estimated at nearly 500,000/year, which represents about 5.3% of the global TB burden\(^3^9\).

The highest rates of MDR-TB were found in China and countries of the Former Soviet Union, while fourteen countries/regions had MDR-TB rates >5% among new cases (see Figure 1 below)\(^4^0\).

**Figure 1: Countries/regions with MDR-TB rates >5% among new TB cases 2002-2006**

A few countries stand out with regards to specific trends in MDR-TB. Increases have been observed in the Republic of Korea, Peru and in Orel and Tomsk Oblasts in the Russian Federation. In Peru, it is suspected that increases in MDR-TB may be a reflection of weaknesses in overall basic TB control, including MDR-TB management, while, in Orel and Tomsk, “it is possible that while susceptible cases are being successfully treated, a sufficient reduction in MDR-TB cases has not been achieved leaving drug resistant cases as an increasing reservoir of TB transmission”\(^4^2\). In Korea, the reasons behind the MDR-TB increase remain unclear\(^4^3\). In Estonia and Latvia, which were considered MDR-TB “hotspots” in 1994, MDR-TB appears to be stabilizing. This stabilization is attributed to a substantial investment and sustained assault on MDR-TB. Finally, decreases in MDR-TB have been observed in both Hong Kong and the United States.
XDR-TB: Extensively drug-resistant TB, or XDR-TB, which is potentially untreatable with currently available drugs, is defined as TB with resistance to any fluoroquinolone and one of the three second-line anti-TB injectables (Amikacin, Kanamycin or Capreomycin) in addition to isoniazid and rifampicin. At least one XDR-TB case was recorded in 45 countries (more than half of those providing data to the report – see Figure 2 below) while, in the former Soviet Union, proportions of XDR-TB among MDR-TB cases range from 4% in Armenia up to almost 24% in Estonia. Based on the data used to inform the report, WHO estimates that approximately 40,000 XDR-TB cases emerge annually.

Other relevant concerns raised by the report include the paucity of available resistance data from many countries. For example, in Africa, the region with the highest TB incidence in the world, only six countries were able to provide input to the report, due to severely limited laboratory capacity and lack of appropriate equipment and trained personnel. As a result, the true magnitude of the MDR and XDR-TB problem in Africa remains unclear. This example highlights the urgent need for strengthening laboratory capacity and training necessary staff to undertake resistance testing on a wider scale.

Another concern raised regards access to testing. Even though rapid MDR-TB diagnostic tests, that take one week, rather than three months, exist, the report highlighted the fact that most patients cannot access them, for a variety of reasons. This point highlights the crucial challenge of strengthening health systems: it is not enough for a rapid test to exist; for patients to benefit access must be facilitated, and (financial and physical) barriers to access minimized.

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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. And this even though few countries are currently able to diagnose XDR-TB! (The WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance. 2008. Anti-tuberculosis drug resistance in the world. Fourth global report).
Drug resistance trends and magnitude in *Vibrio cholerae*

There have been a minimum of seven cholera pandemics in recent history\(^9\). While management of the disease through prompt oral rehydration therapy rather than antibiotic treatment is the usual recommendation, given the pandemic nature of the *V. cholerae*, the causative agent of cholera, antimicrobials are often used to shorten the course of infection and prevent person-to-person transmission\(^{50}\). Antimicrobials are also usually a crucial component of cure in malnourished or immunocompromised patients\(^{51}\).

Resistant strains of *V. cholerae* are found wherever cholera is endemic. Owing to better laboratory capacity in Asia, more studies were available and all known resistance mechanisms in cholera were documented in Asia before they were seen elsewhere\(^{52}\). Studies on importations of resistant strains to the US also suggest that, during the 1990s, resistant *V. cholerae* predominantly came from Asia and Latin America\(^{53}\). Cholera currently appears to be less common in Asia and Latin America than in Africa but underreporting from all regions is a documented problem\(^{54}\). Resistance is most certainly more commonplace in Africa than the published literature suggests\(^{55}\).

Drug-resistant *V. cholerae* carrying resistance plasmids have been reported from Asian countries such as India, Bangladesh, Vietnam and Thailand and also from Peru\(^{56}\). Strains of *V. cholerae* resistant to tetracycline (which was the cholera treatment of choice for many years) emerged during the late 1970s in Tanzania, Kenya and other parts of Africa\(^{37}\). Other drugs (see Table 4 below for an overview of drugs used to treat cholera) now commonly used to treat cholera infection include trimethoprim-sulfamethoxazole and, more recently, fluoroquinolones, given the emergence and spread of trimethoprim-sulfamethoxazole-resistant strains. As with antimalarial-resistant parasites and drug-resistant *S. dysenteriae*, emergence of resistance in *V. cholerae* has been linked to increased mortality rates in recent African outbreaks\(^{58}\). Indeed resistant strains of *V. cholerae* played a considerable role in recent outbreaks in Goma\(^{59},^\text{z}\) (in 1994 which resulted in approximately 12,000 Rwandan deaths) and in a Guinea-Bissau outbreak\(^{60,\text{aa},\text{bb}}\).

\(^7\) While originally called “Asiatic cholera,” the focus of the pandemic now is Africa where two-thirds of cholera pandemics have occurred during the past decade (Griffith DC, Kelly-Hope LA, Miller MA. Review of reported cholera outbreaks worldwide, 1995–2005. Am J Trop Med Hyg. 2006;75:973–7)


\(^\text{aa}\) One unique factor about the Guinea Bissau outbreak is that it was investigated at the molecular level. When this does not occur, similar resistant-strain outbreaks could be happening elsewhere undetected. For example, there is data from Zambia that suggests that this is the case (see Mwansa, J. C., J. Mwaba, C. Lukwesa, N. A. Bhuiyan, M. Ansaruzamman, T. Ramamurthy, M. Alam, and G. Balakrish Nair. 2006. Multiply antibiotic-resistant Vibrio cholerae O1 biotype El Tor strains emerge during cholera outbreaks in Zambia. Epidemiol Infect:1-7.).

\(^\text{bb}\) The Guinea-Bissau outbreak occurred in two phases, from 1996-1997 and 1997-1998. While there was no evidence of resistant strains during the first phase, multi-resistant strains featured prominently during the second phase. The presence of the resistant strain is thought to have been a major factor in the marked increase in deaths during the second phase as compared to the first (Dalsgaard A, Forslund A, Petersen A, Brown DJ, Dias F, Monteiro S, et al. Class 1 integron-borne, multiple-antibiotic resistance encoded by a 150-kilobase conjugative plasmid in epidemic *Vibrio cholerae* O1 strains isolated in Guinea-Bissau. J Clin Microbiol. 2000;38:3774–9 cited in IN Okeke, OA Aboderin, DK Byarugaba, KK Ojo and JA Opintan. Growing problem of multidrug-resistant enteric pathogens in Africa. Emerging Infectious Diseases. Vol. 13, No 11, November 2007)
Table 4: Drugs used to treat cholera and year introduced

<table>
<thead>
<tr>
<th>Antibacterial drug class</th>
<th>Year introduced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracyclines</td>
<td>1950</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>1968</td>
</tr>
<tr>
<td>Quinolones</td>
<td>1962</td>
</tr>
</tbody>
</table>

Drug resistance trends and magnitude in Shigella

There are four species of *Shigella: dysenteriae, flexneri, boydii* and *sonnei*, with *dysenteriae* and *flexneri* being the most common in developing countries. *Shigella*, which is extremely contagious and lethal in 5-15% of cases if no effective treatment is available, is estimated to result in ~600,000 deaths/year, primarily among children. Antibiotics are the first line of treatment for *Shigella* and prompt treatment is required. In the absence of treatment, *Shigella* carriage may be up to several weeks, allowing for increased transmission.

*Shigella* resistance has been reported to trimethoprim-sulfamethoxazole, ampicillin, tetracycline and chloramphenicol (see Table 5 below which lists antibiotics used against *Shigella*). In the 1990s, resistance began to emerge and included some fluoroquinolones and some third-generation cephalosporins; resistance also has increasingly been seen to nalidixic acid. The only remaining drugs to which most *Shigella* remain sensitive, ciprofloxacin and ceftriaxone, are relatively expensive and often not available. Additionally there is evidence of resistance emerging to them as well; indeed resistance to ciprofloxacin has also been reported. Resistance has been linked to higher death rates (primarily among children) from *S. dysenteriae* type 1.

*Shigella* resistance was reported earlier in Asia than in other parts of the world, is better documented there and remains very common in some Asian countries (such as Bangladesh, Indonesia and Thailand). Indeed multi-drug resistant *Shigella* was already a phenomenon in Bangladesh over one decade ago: a 1997 study found that 100% of *S. dysenteriae* isolates were resistant to ampicillin, tetracycline, and chloramphenicol; while 93% were resistant to ampicillin, tetracycline, chloramphenicol, TMP-SMX, and nalidixic acid. In Africa, *Shigella dysenteriae* has been responsible for large epidemics, including Malawi in 1992 and 1993 and Burundi in 1994.

Several small-scale studies in Africa have observed that the prevalence of *Shigella* appears to have either remained constant or dropped over the last 20-30 years. However, MDR strains are on the rise so that resistance may be a principle reason for the present-day burden from *Shigella*. Importantly, in many cases, treatment guidelines have not changed over this period even though the pathogen clearly has. The scattered reporting through small studies therefore has highlighted the problem but has not resulted in changes in policy, as modification of treatment guidelines typically requires evidence from larger population-based studies. This is an important example of the consequences of surveillance shortfalls.

Table 5: Drugs used against Shigella and year introduced

<table>
<thead>
<tr>
<th>Antibacterial (such as ceftriaxone)</th>
<th>Year introduced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>1945</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>1949</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>1950</td>
</tr>
<tr>
<td>Fluoroquinolones (such as ciprofloxacin)</td>
<td>1960s</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>1961</td>
</tr>
<tr>
<td>Quinolones (such as nalidixic acid)</td>
<td>1962</td>
</tr>
</tbody>
</table>

These data should be interpreted as anecdotal information given the size of these studies: small studies are prone to error, particularly if there are seasonal effects or specific risk groups and *Shigella* probably has both (Iruka Okeke, Personal communication and Vargas, M., J. Gascon, C. Casals, D. Schellenberg, H. Urassa, E. Kahigwa, J. Ruiz, and J. Vila. 2004. Etiology of diarrhea in children less than five years of age in Ifakara, Tanzania. Am J Trop Med Hyg 70:536-9). In the absence of surveillance data, a meta-analysis may be useful.

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Recent regional/country-specific data includes the following:

In the United States, a 2006 review\textsuperscript{72} of 1,604 \textit{Shigella} isolates\textsuperscript{44} collected by the National Antimicrobial Resistance Monitoring System (NARMS) for Enteric Bacteria over 1999-2002, found evidence of large increases in resistance among all \textit{Shigella} strains in the United States, namely:

- Ampicillin-resistant \textit{Shigella} strains increased from 32\% in 1986, to 67\% in 1995 to 78\% of all isolates over the 1999-2002 period
- Trimethoprim-sulfamethoxazole (TMP-SMX)-resistant \textit{Shigella} strains increased from 7\% in 1986, to 35\% in 1995 to 46\% over the 1999-2002 period
- One percent of \textit{S. sonnei} and 2\% of \textit{S. flexneri} isolates were resistant to nalidixic acid, while one \textit{S. flexneri} isolate was resistant to ciprofloxacin

Some examples from developing country-specific studies show that resistant \textit{Shigella} is a global concern:

- \textit{S. sonnei} is a considerable problem in some areas in Asia and drug-resistant acquired strains of \textit{S. sonnei} have been found in Japanese travelers. These strains were acquired while the travelers were in Indonesia, Thailand and India and 80-90\% of strains were resistant to two or more antibiotics\textsuperscript{73}
- One study\textsuperscript{74} in Uganda found that none of the \textit{Shigella} isolates were sensitive to TMP-SMX, while only 33.4\% were to ampicillin (which are the two antibiotics recommended for treatment of non-epidemic dysentery in Uganda). Low levels of resistance to nalidixic acid were also reported, while all isolates were sensitive to fluoroquinolones
- Trend data from the International Centre for Diarrheal Disease, Bangladesh (ICDDR,B)\textsuperscript{75} reveals an increase in ampicillin-resistant \textit{Shigella} (all \textit{Shigella} species) from 10\% of all isolates in 1982 to 57\% in 1991; this increase was from 4\% to 83\% for \textit{S. dysenteriae}. During the same period, TMP-SMZ resistance increased from 1\% to 56\% for all \textit{Shigella} species and from 4\% to 83\% for \textit{S. dysenteriae}

\textit{S. pneumoniae} is thought to cause up to 70\% of the more than 3 million child deaths/year attributed to bacterial acute respiratory infections; in addition it is responsible for otitis media, bacteremia and bacterial meningitis in children\textsuperscript{76}. Recent studies indicate that penicillin-susceptible strains of \textit{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 especially important as penicillin-resistant strains have been shown to be more likely to be resistant to other antibiotics as well\textsuperscript{77}. Multi-drug resistant \textit{S pneumoniae} clones have been isolated that are resistant to penicillin, chloramphenicol, tetracycline and erythromycin; these clones are now thought to be widespread and predominant\textsuperscript{78} (see Table 6, below which lists antibiotics used against \textit{S. pneumoniae}).

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<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Year introduced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>1941</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>1949</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>1950</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>1952</td>
</tr>
<tr>
<td>Fluoroquinolones (such as ciprofloxacin)</td>
<td>1960s</td>
</tr>
</tbody>
</table>

Some evidence also exists indicating that \textit{S. pneumoniae} resistance may be more frequently encountered in urban areas than in rural settings; it is hypothesized this is largely attributable to the greater accessibility of antimicrobials in cities.\textsuperscript{79} It also can be due to the fact that crowding is more prominent in urban areas so increased transmission might be a factor, as might access to international clones due to port proximity.\textsuperscript{80}

\textsuperscript{44} 80\% of which were \textit{S. sonnei}, 18\% \textit{S. flexneri}, 1\% \textit{S. boydii} and 0.4\% \textit{S. dysenteriae}
The Alexander Project, a global level program seeking to quantify the *S. pneumoniae* resistance problem by gathering country-specific data, found high levels of drug resistance throughout the world, with Asia being a particular concern (see Table 7 below).

**Table 7: Prevalence of *S. pneumoniae* resistant to three or more drug classes, Alexander Project 1998-2000**

<table>
<thead>
<tr>
<th>Region</th>
<th>Number</th>
<th>% resistant to any three drug classes, excluding penicillin</th>
<th>% resistant to any three drug classes, including penicillin</th>
<th>% resistant to any four drug classes</th>
<th>% resistant to any five drug classes or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>540</td>
<td>14.3</td>
<td>24.8</td>
<td>13.5</td>
<td>3.3</td>
</tr>
<tr>
<td>East Europe</td>
<td>1109</td>
<td>10.1</td>
<td>11.7</td>
<td>6.0</td>
<td>1.0</td>
</tr>
<tr>
<td>West Europe</td>
<td>3328</td>
<td>14.7</td>
<td>18.4</td>
<td>11.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Far East</td>
<td>730</td>
<td>53.2</td>
<td>63.2</td>
<td>40.6</td>
<td>23.0</td>
</tr>
<tr>
<td>Middle East</td>
<td>314</td>
<td>11.2</td>
<td>18.2</td>
<td>10.5</td>
<td>4.1</td>
</tr>
<tr>
<td>Latin America</td>
<td>429</td>
<td>13.3</td>
<td>20.1</td>
<td>12.1</td>
<td>1.9</td>
</tr>
<tr>
<td>USA</td>
<td>8882</td>
<td>17.5</td>
<td>23.7</td>
<td>14.6</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Additional recent regional and country-specific data includes the following:

**Europe:**
- In 2003, over 25% of strains were penicillin-resistant.
- In 2002, the proportion of penicillin non-susceptible *Streptococcus pneumoniae* (PNSP) was over 25% in France, Israel, Poland, Romania and Spain, the highest percentage being in France at 53%.
- In some places, notably Scandinavia and the Netherlands, resistance levels have remained low, at only 1-2%.

**Americas:**
- In the United States in 2005, up to 40% of infections caused by *S. pneumoniae* are the result of strains resistant to at least one drug while 15% of infections are the result of strains resistant to three or more drugs. Resistance is most common in the southern parts of the US.

**Asia:**
- During 2000-2001 *S. pneumoniae* isolates from Viet Nam showed the highest prevalence of penicillin resistance (71%), followed by those from the Republic of Korea (55%), China, Hong Kong (43%), and Taiwan, China (39%); there was also high resistance reported from Japan.
- Isolates from Viet Nam also showed the highest resistance to erythromycin (92%), followed by Taiwan, China (86%), the Republic of Korea (81%), Hong Kong (77%), and the People’s Republic of China (excluding Taiwan and Hong Kong) (74%).
- Isolates from Hong Kong showed the highest rate of ciprofloxacin resistance (12%), followed by Sri Lanka (9.5%), the Philippines (9.1%), and the Republic of Korea (6.5%).

**Malaria drug resistance magnitude and trends**

The two most common types of malaria parasites -- *P. falciparum* and *P. Vivax* -- exhibit resistance to drugs. See Table 8 below for the year each antimalarial drug was introduced and when resistance to it was documented. As previously mentioned, resistance in *P. falciparum* has emerged to all classes of...
antimalarials to date, except for the ACTs. Less is known about resistance in *P. Vivax*; however both chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) resistance have been reported.

### Table 8: Drugs used to treat malaria and year introduced

<table>
<thead>
<tr>
<th>Anti-malarial drug</th>
<th>Year introduced</th>
<th>Year resistance first noted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine phosphate</td>
<td>1945</td>
<td>1957</td>
</tr>
<tr>
<td>Quinine</td>
<td>1632</td>
<td>1910</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>1977</td>
<td>1982</td>
</tr>
<tr>
<td>Primquine phosphate</td>
<td>1926</td>
<td>1949</td>
</tr>
<tr>
<td>Proguanil</td>
<td>1948</td>
<td>1949</td>
</tr>
<tr>
<td>Sulfadoxine-pyrimethamine</td>
<td>1967</td>
<td>1967</td>
</tr>
<tr>
<td>Artovaquone</td>
<td>1996</td>
<td>1996</td>
</tr>
<tr>
<td>Artemisinin Combination Therapies (ACTs)</td>
<td>2001</td>
<td></td>
</tr>
</tbody>
</table>

Chloroquine resistance emerged in *Plasmodium falciparum* over a half-century ago (by the end of the 1950s), almost simultaneously in South America (Colombian/Venezuelan border) and South East Asia (Thai/Cambodian border), in both cases where uncontrolled CQ use was rampant among communities with poor routine health service access. Resistance spread across Africa (especially East Africa) by the late 1970s and on to other parts of Africa during the 1980s (see Figure 3 below). *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.

![Global spread of chloroquine-resistant strains of *P. falciparum*](image)

East Africa, South Asia, South-East Asia, Oceania, the Amazon Basin and some coastal areas in South America all have high levels of CQ resistance. In many East African countries, CQ fails to treat more than 50% of patients. Country-specific data from Africa reveal the highest levels of CQ-resistance for that continent to be in Ethiopia, Gabon, Burundi and Eritrea (see Figure 4, below).

CQ resistant strains of *Plasmodium Vivax*, which is less severe and generally does not result in death and which has been less studied, have also been reported in Brazil, Colombia, Guatemala, Guyana, Peru,
Irian Jaya and Papua New Guinea. Only strains from Central America north of the Panama canal and in Haiti and the Dominican Republic were fully susceptible to CQ at the beginning of the 21st century.

High-level CQ resistance has prompted several African countries (Tanzania, Malawi, and South Africa) to switch to sulfadoxine–pyrimethamine (SP), one of the first successors to chloroquine, as the first-line drug. Resistance to SP, however, emerged within 5 years of extensive use (current levels of resistance to SP vary dramatically by country depending on historical treatment protocols) and, as noted in Table 9 below, is already reaching 10-20% in some African countries. Indeed, in southern Ethiopia in 2005 extraordinarily high frequency of drug-resistant mutations was found in both P. vivax and P. falciparum to both chloroquine and SP. High levels of SP resistant P. falciparum are also found in South-East Asia and the Amazon basin.

P. falciparum resistance to mefloquine and to quinine has also been reported in Southeast Asia, in particular in border areas around Cambodia, Myanmar and Thailand. Resistance to mefloquine has also been found in Brazil. Moderate to high levels of amodiaquine-resistant P. falciparum have also been reported from East Africa, the Amazon basin and Papua New Guinea.

Table 9: Global Levels of Drug-Resistant P Falciparum

<table>
<thead>
<tr>
<th>Region</th>
<th>Resistant to chloroquine</th>
<th>To SP</th>
<th>To both chloroquine and SP</th>
<th>To mefloquine</th>
<th>To amodiaquine</th>
</tr>
</thead>
<tbody>
<tr>
<td>East Africa</td>
<td>~50-60%</td>
<td>~10-20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central Africa</td>
<td>~50-60%</td>
<td>~10%</td>
<td></td>
<td></td>
<td>“Low”</td>
</tr>
<tr>
<td>Southern Africa</td>
<td>~10-30%</td>
<td>~10-20%</td>
<td></td>
<td></td>
<td>“Low”</td>
</tr>
<tr>
<td>West Africa</td>
<td>~10-30%</td>
<td>~10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Six African countries†</td>
<td></td>
<td>~3-13%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>Generally above 40%</td>
<td>Below 20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western Pacific</td>
<td>Generally above 40%</td>
<td>~20-40%</td>
<td></td>
<td>Between 10-20%</td>
<td></td>
</tr>
<tr>
<td>South East Asia</td>
<td>~40%</td>
<td>Around 20%</td>
<td></td>
<td>More than 20%</td>
<td></td>
</tr>
<tr>
<td>South America</td>
<td>Over 80%</td>
<td>Close to 20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central America</td>
<td>Over 80%</td>
<td>~10%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Comoros, Eritrea, Rwanda, Sudan, Uganda and Zimbabwe
Over the past decade, countries in which resistance to CQ is high and/or where additional resistance (to SP and/or mefloquine) exists have introduced combination treatment for malaria that includes the plant artemisinin (artemisinin combination therapies, or ACTs). Since 2001, a total of 56 countries worldwide had adopted ACTs, most as first-line therapy, but some as second-line. In 2003, the WHO issued guidelines urging ACTs as first-line treatment, and requesting countries and companies to cease offering monotherapy.

To date, in vitro sensitivity of ACTs has been reported; however there is no confirmed evidence of in vivo artemisinin-resistant *P. falciparum*. Table 10, below, summarizes regional and country-specific areas of known high resistance across pathogens.

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This is in line with recent WHO recommendations that “treatment policies for falciparum malaria in all countries experiencing resistance to monotherapies, such as chloroquine, sulfadoxine/pyrimethamine and amodiaquine, should be combination therapies, preferably those containing an artemisinin derivative (ACT - artemisinin-based combination therapy)” (Roll Back Malaria/WHO. Malaria Control Today. Current WHO recommendations. Working document. March 2005).

To date, about half of the manufacturers of artemisinin-based drugs have complied with these guidelines.

Of the 56 countries which have adopted ACTs, 25 are currently deploying them. In Africa countries include: Burundi, Comoros, Ethiopia, Liberia, Mozambique, Sao Tome and Principe, Sierra Leone, South Africa, Sudan, Zambia, and Zanzibar. Countries outside of Africa which are deploying ACTs include: Bangladesh, Bolivia, Cambodia, Ecuador, Guyana, Indonesia, Lao PDR, Myanmar, Papua New Guinea, Peru, Philippines, Surinam, Thailand, and Viet Nam.

The original aim was to develop a “hot spot” map highlighting areas of high resistance. However the Working Group felt that pinpointing resistance in this way is unnecessary and possibly unhelpful as such a mapping may be more influenced by surveillance capacity than actual location of disease emergence. Additionally, a mapping based on where resistance information is known could be interpreted as assigning blame to some countries or regions for not adequately preventing resistance. This underscores the need to use data cautiously and generally rely on localized information, rather than meaningless aggregations.
<table>
<thead>
<tr>
<th>Table 10: Some examples of identified geographical areas of relatively high resistance prevalence by disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>M. tuberculosis (2002-2006 data unless otherwise referenced)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>P. falciparum and P. vivax</td>
</tr>
<tr>
<td>In Africa</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>S. dysenteriae</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>V. cholerae</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>S. pneumoniae</strong></td>
</tr>
<tr>
<td>• South Africa</td>
</tr>
</tbody>
</table>

\footnote{109} Although antimicrobials are often used despite the fact that they are not required to treat cholera, research and public health studies often ignore resistance (Iruka Okeke, personal communication) - for example, one important recent review of the upsurge of cholera in Africa does not even mention resistance (Gaffga, N. H., R. V. Tauxe, and E. D. Mintz. 2007. Cholera: a new homeland in Africa? Am J Trop Med Hyg 77:705-13.11). Therefore the paucity of data on susceptibility is more marked with cholera than with many other diseases (Iruka Okeke, personal communication).
Classifying the factors that drive drug resistance

What is meant by “factors” that drive drug resistance? And how should we think about these factors? Our goal in this paper is to approach the issue from multiple perspectives, rather than adopt a linear one-dimensional approach. We classify resistance drivers broadly into three key categories; however we do not only consider these categories as “stand alone,” but we also seek to determine how they interact to drive resistance. The goal is to identify where and how among the many “decision-points” that affect drug resistance is the most realistic and feasible chance to exert influence and impact policy.

We identify three categories of resistance drivers:

1) Drug and drug technology issues -- how drugs are developed and manufactured and how this can affect their propensity to drive resistance. For example, the half-life of drugs and how drugs respond to selection pressure.
2) Health systems issues – how drugs are selected and conveyed through the health system, for example, can create opportunities for resistance to develop.
3) Behavioral issues - primarily concerning choices and use of drugs by the provider and patient.

Figure 5 depicts how these three sets of factors converge to drive resistance development.

In addition to these three groups of factors, societal level “exacerbating factors” (such as poor hygiene, poor sanitation, unreliable water supply, civil conflict etc.) should be acknowledged; however this paper will not address these factors at any length, as they are well beyond its scope.

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Sanitation is a more of a structural factor, while hygiene is to some extent behavioral. Therefore, although interventions to correct sanitation deficiencies may end up being more expensive, their outcomes are probably more predictable (Iruka Okeke, personal communication).
What factors drive drug resistance?

Drug and drug technology characteristics

Conditions of the drugs themselves can also favor resistance development. This section highlights those most crucial to the pathogens we are addressing.
Resistance is favored by a longer drug half-life

A longer drug half life is argued to improve patient adherence, as treatment can be given in a directly-observed short regimen or even sometimes as a single dose\textsuperscript{110}. SP (which has a long half-life) provides the additional advantage that it may help patients recover from anemia, a common by-product of malaria infection\textsuperscript{111}. The concern with using drugs that have long half-lives is that, when their concentrations drop, they retain effectiveness against re-infection by drug-sensitive parasites but are not effective against resistant parasites – thus in fact allow resistant strains to proliferate and contributing to the spread of resistance\textsuperscript{112}. Even when the concentrations of these drugs are high, they will not protect against infections with highly resistant organisms.

Monotherapy favors acquired resistance; fixed-drug combinations (FDCs) can be an effective “resistance-slowing” tool

Fixed-drug combinations, which usually include drugs with different targets, are commonly used in TB treatment and in ART therapy\textsuperscript{on}. Particularly with the advent of several artemisinin combination therapies (ACTs), FDCs have been shown to be effective in slowing malaria parasite resistance and reducing malaria incidence\textsuperscript{113,oo}. FDCs slow resistance development through decreased probability that a resistant variant will arise. In the case of malaria for example, where resistance “results from spontaneous genetic mutations, the chance that a parasite will emerge that is simultaneously resistant to

\textsuperscript{on} Indeed the higher levels of ART resistance in the Western world are usually attributed partially to the fact that monotherapy was the standard for several years prior to the advent of HAART. In contrast, most individuals on ART treatment in developing nations began with combination therapy.

\textsuperscript{oo} However, many of the drugs currently being introduced as fixed-combinations with artemisinin have much longer half-lives than artemisinin. This most likely is not a concern in low malaria parasite transmission areas but may be a problem in areas where transmission is high, as, once artemisinin has been fully eliminated, partially or fully resistant parasites would be exposed to sub-therapeutic levels of the partner drug and be selected for (Talisuna AO, Bloland P, D'Alessandro U: History, dynamics, and public health importance of malaria parasite resistance. \textit{Clin Microbiol Rev} 2004, 17:235-254. 3. World Health Organization).
two drugs with unrelated modes of action (that is, drug targets) is the mathematical product of the individual parasite mutation frequencies multiplied by the total number of parasites exposed to the drugs.\textsuperscript{114}

\textit{Resistance within and across classes of drugs}

In some cases, resistance developed against one drug results in a degree of or total resistance to other drugs within the same drug class (resistance, in fact, is thus against a mode of action), a phenomenon called cross resistance. This phenomenon is particularly important for first-generation NNRTIs for HIV therapy and among drug classes used to treat \textit{Shigella} strains. In addition to cross resistance within and between classes, there is also the concern that some antimalarials and antibacterials can exert selective pressure on another class of pathogens (examples include sulfadoxine-pyrimethamine and cotrimethoxazole, as well as tetracycline, which has been combined with quinine for malaria).\textsuperscript{115}

Promotion of prophylaxis against opportunistic infections in AIDS patients has meant widespread increased use of medicines, in particular antibiotics. There is good evidence that this prophylaxis has prevented many individuals from dying -- for example, there is overwhelming evidence suggesting that TMP-SU prophylaxis improves survival among AIDS patients without access to ARVs.\textsuperscript{117} Indeed, to date, most of the literature - primary research and reviews - focuses on impact on survival and the low cost of TMP-SU, and does not address the problem of resistance.\textsuperscript{118} Of the few studies that do take resistance in account, a few found no impact on resistance while more found an association of TMP-SU prophylaxis with resistance (the larger more long-range studies seemed to be more likely to find an association with resistance).\textsuperscript{120} Therefore, while prophylaxis clearly is saving lives, it seems it should also be a priority to monitor the impact of increased use on resistance development.

\textit{Length and complexity of treatment: impact on adherence and resistance selection pressure}

Longer and more complex treatment may impact adherence, as can drug cost and side effects. For HIV positive individuals on ART, resistance is more likely to arise if optimal drug doses are not maintained, which can occur if adherence is poor.\textsuperscript{121} Evidence supporting the relationship between adherence and resistance emergence in the treatment of chronic infections such as tuberculosis (TB) is much stronger than in the treatment of acute and largely self-limiting infections.\textsuperscript{122,91} Indeed, as long as patients adhere appropriately, there is evidence supporting the idea that, when compared with longer courses, shorter antibiotic courses may actually select for less resistance in pneumococcus.\textsuperscript{123}

The length of treatment for the given illness helps define which adherence interventions are most appropriate, although it is always useful to look at the given context before designing and implementing

\textsuperscript{90} Defined as doses that reduce viral load to less than approximately 50 to 200 HIV RNA copies/mL. Indeed, “If a drug completely stops viral replication, resistance should not appear. In contrast, a drug with minimal potency will not exert sufficient selective pressure to generate resistance. The ideal circumstances in which resistance will occur arise where potent antiviral agents are used sub-optimally, e.g. as monotherapy or dual therapy for HIV, or where there is poor drug compliance” (Department of Health United Kingdom. The path of least resistance: main report of the Standing Medical Advisory Committee, Sub-Group on Antimicrobial Resistance. London: Department of Health, 1998.)

\textsuperscript{91} This is an example of how selection pressure differs among pathogens: “It is likely that resistance selection occurs more readily in the commensal flora (for example, the pneumococcal flora of the nasopharynx) than among the organisms causing the acute infection. Thus, shorter courses (and reduced compliance) may reduce the selection of resistance in commensal flora. In contrast, in TB, selection takes place in the infecting pathogen, and poor compliance is associated with the selection of resistant strains.” (Laxminarayan, R. et al. 2006. “Drug Resistance.” Disease Control Priorities in Developing Countries, 2nd ed., ed. D.T. Jamison, J.G. Breman, A.R. Measham, G. Alleyne, M. Claeson, D.B. Evans, P. Jha, A. Mills, and P. Musgrove, 1031-51. New York: Oxford University Press. http://www.dcp2.org)
any intervention. For shorter antibiotic courses of 5-7-10 days, simple changes in policy may be all that is required, such as not requiring a patient to return to the hospital to collect the second half of his/her treatment course or mandating (and enforcing) that prescribers prescribe a full course of treatment, alongside clear guidelines that the course must be fully completed. For longer treatments, such as for TB, incentives and enablers that compensate for time off work (such as transport vouchers or food parcels) have been shown to be effective, while another option is bringing the drug closer to the patient’s community (place of work or home) so that travel, time and other costs are decreased. As Table 11 below shows, interventions to improve ART adherence tend to be more complex, give the nature of the treatment regimen: the fact that it is life-long and there are considerable side-effects. Some of the interventions are also applicable to other diseases, in particular TB.

Table 11: Interventions to improve adherence to ART medications

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Remarks and examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-focused</td>
<td></td>
</tr>
<tr>
<td>• Education</td>
<td>Increase knowledge about disease and treatment regimen and effectiveness; clarify instructions</td>
</tr>
<tr>
<td>• Cues and reminders</td>
<td>Use unit-dose packaging; encourage pill sorting; plan doses to coincide with daily habits</td>
</tr>
<tr>
<td>• Involvement in therapeutic plans</td>
<td>Tailor drug regimen to patient lifestyle with attention to both dosing schedule and side effects</td>
</tr>
<tr>
<td>• Rewards and reinforcement</td>
<td>Improved health; improved surrogate markers (CD4+ cell counts and/or virus load if available); check medication at visit</td>
</tr>
<tr>
<td>• Treatment of depression, substance abuse, and co-morbid conditions</td>
<td>Provide peer counseling and support groups, buddy plans, case management, home visits, phone-based or pharmacy-based interventions, directly observed therapy</td>
</tr>
<tr>
<td>• Social support or extended supervision</td>
<td>Provider focused</td>
</tr>
<tr>
<td>• Continuing medical education</td>
<td>Provide programs to reinforce the central importance of adherence, to improve clinician communication, and to improve competence with side-effect management</td>
</tr>
<tr>
<td>• Cues and instruments</td>
<td>User-friendly medication and review forms and patient-education aids</td>
</tr>
<tr>
<td>• Additional support</td>
<td>Adherence counselors and case managers</td>
</tr>
<tr>
<td>Regimen-focused</td>
<td></td>
</tr>
<tr>
<td>• Decreased daily frequency of dosing</td>
<td></td>
</tr>
<tr>
<td>• Decreased pill burden</td>
<td></td>
</tr>
<tr>
<td>• Improved taste/palatability</td>
<td></td>
</tr>
<tr>
<td>• Decreased side-effects</td>
<td></td>
</tr>
<tr>
<td>• Decreased cost</td>
<td></td>
</tr>
</tbody>
</table>

Inappropriate dosage levels are not always due to poor adherence. As mentioned above, low doses of a given drug can result from counterfeit drugs that contain less active ingredient than mandated or from drugs that originally contained the full active ingredient but, due to poor transport and storage conditions, now contain sub-therapeutic levels. Simple human error also can be at fault. For example, it has recently been found that the standard recommended dose for sulfadoxine-pyrimethamine in children was too low (by about half!); massive systematic underdosing almost certainly contributed to rapid resistance development.

Absolute levels of drug use, fitness and virulence

In the industrialized world, it has long been argued that absolute levels of drug use drive resistance development (for example, see Figure 6 below, showing a clear relationship between increased antibiotic consumption and increased levels of resistance in pneumococci).
However it is not so clear that this argument also holds true in the developing world. While it has been argued that increasing use of antibiotics and antimalarials facilitates selection of resistant strains, to date the evidence of this is less strong in developing countries, due to a lack of data on antibiotic use.

What does seem clear is that the link between resistance and use is most obvious when resistance arises through mutation and can be selected for during individual therapy (i.e., when adherence is poor or the drug contains substandard levels of active ingredient), resulting in clinical failure.

What happens when drug use decreases? In the absence of drug selection pressure, does the resistant organism grow at a faster rate than susceptible ones? Mathematical modeling has predicted that resistance rates decline more slowly than they emerge. Additionally it has been shown that declines in resistance are usually faster in hospital-acquired infections than in community-acquired ones, and that this is most likely due to the fact that fitness costs are higher in the community. Fitness is a highly complex issue and one that this paper will not attempt to consider further.

There are several other important drug- and pathogen-related considerations which contribute to the development of drug resistance. For example, what patient-related immunologic factors lead to faster or slower resistance development? Additionally, are there variations in virulence of drug-resistant mutants and in the rates of persistence of resistant populations once drug use has stopped? In the case of *S. pneumoniae*, it is commonly assumed that drug resistant *S. pneumoniae* (DRSP) strains do not compete as well and will therefore recede in the absence of antibiotic exposure. This assumption has given rise to

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It is important to understand the incentives in this environment. Where controls have been strict and effective, such as in the Netherlands, they have also meant a cut in drug company profits due to lower prescribing levels. This has also resulted in less need for a second generation product (K. Outterson, personal communication).

campaigns for more judicious use of antibiotics (see mention to Finland and Iceland above). …Indeed, both clinical isolates and laboratory derived mutants with alterations in penicillin-binding proteins conferring resistance to penicillin have shown defective growth in drug-free medium and reduced virulence in mouse models. However, to date, there is no convincing clinical evidence that the prevalent DRSP strains have reduced virulence133.”

Possibility that pathogen will “re-sensitize” to a given drug

Some pathogens, in the absence of a given drug will, over time, “re-sensitize” to that drug, a biological fact that drives policy arguments promoting drug cycling strategies. How organisms “re-sensitize” is not fully understood; however it is clearly related to the genetic mechanism for resistance and therefore it is too simplistic to expect a pathogen to respond in a similar fashion each time, unless resistance mechanisms are not different134. For example, if mutation towards resistance is not accompanied by subsequent mutations to increase fitness, removal of selective pressure could lead to the replacement of the resistant strain with sensitive ones135. One example is the return of malaria sensitivity in Kenya136. However, if resistance is acquired on a horizontally-transferred genetic element that carries multiple resistance genes, removal of a drug will not lead to disappearance of resistance if other drugs encoded on the element are still in use137. Examples include sulphonamide resistance in the UK138 as well as the extremely rare ability of Shigella strains to regain sensitivity139.

It has been hypothesized that the potential for restoration varies dramatically by pathogen and setting (community vs. institution)140. Modeling has provided some clues about resistance persistence but models are yet to incorporate genetic information, which is expected to be rather complex, particularly as not enough is known from the biological point of view141.

Do alternatives to using antimicrobial or antivirals exist?

Vaccines have been shown to work as an effective tool to slow resistance development. Vaccine development and deployment can affect resistance in two ways: the more broadly applicable strategy is to use vaccines to reduce the overall infectious disease burden and therefore the selective pressure from antimicrobials while the more narrow approach is to use vaccines that specifically protect against drug resistant clones142. To illustrate the former, use of the Hib vaccine in the Gambia significantly reduced H. influenzae infection and related deaths, while simultaneously decreasing the need for broad spectrum antimicrobial therapy in the children typically affected by the disease143.

Box 2: The potential of a cholera vaccine in decreasing disease and antimicrobial use144

Vaccination at time of outbreaks in cholera epidemics or complex emergencies could be used to control outbreak size instead of, or alongside, antimicrobial chemotherapy. For this purpose, even vaccines with short durations of protection (such as those licensed for travelers, which otherwise are not very useful in endemic areas) could achieve the more modest objective of containing an outbreak145. Vaccines are certainly preferable to prophylactic antimicrobial chemotherapy. They require logistical support and advance preparedness needed to contain outbreaks, which may explain why they have rarely been used in this regard.

Promising findings from industrialized countries with traditionally high pneumococcal resistance prevalence (such as France, Spain, Israel and the United States) give hope that disease from a resistant strain will fall once a vaccine that specifically protects against drug-resistant clones is introduced146. Additionally, given that children have long been suspected to be the source of transmission of resistant
*S. pneumoniae* strains to adults, it is interesting to note that introduction of the *S. pneumoniae* conjugate pneumococcal vaccine in 2000 in the US to children resulted in greatly decreased resistance levels among the adult population. Additionally, as there is an association among children between being HIV positive and carrying resistant strains of *S. pneumoniae*, this vaccine could be a powerful and effective tool to slow *S. pneumoniae* resistance among both children and adults in developing countries where HIV is widespread.

Table 12 below highlights drug and drug technology drivers of resistance across diseases.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Drugs for which long half-life is a concern</th>
<th>Factors around Fixed-Drug Combinations (FDCs)</th>
<th>Cross resistance exists across and/or within drug class</th>
<th>Length/complexity of treatment as a driver of poor adherence and resistance selection</th>
<th>Evidence that total use drives resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Widely used in 1st line treatment</td>
<td>Within drug class and across drug class are both concerns</td>
<td>A critical concern</td>
<td></td>
<td>A critical concern</td>
</tr>
<tr>
<td></td>
<td>Second-line ARVs (including protease inhibitors) are not generally available in generic or FDC form</td>
<td>Mono-resistance to Rifampin is rare</td>
<td></td>
<td>This is tough to find evidence for, except at the extreme, given that such a high fraction of antimalarials are taken with absolutely no oversight on dose or compliance to correct intervals etc. As a result, complex antimalarial regimens are particularly problematic</td>
<td></td>
</tr>
<tr>
<td>TB</td>
<td>Rifampin</td>
<td>Widely used in both 1st and 2nd line treatment</td>
<td>A concern, even for a 3 day regimen, if it is a complex regimen. Treatment is almost never observed after the first dose. Additionally, a huge fraction of antimalarials are taken outside the health system and treatment, in this case, is never observed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mono-resistance to Rifampin is rare</td>
<td></td>
<td>This is tough to find evidence for, except at the extreme, given that such a high fraction of antimalarials are taken with absolutely no oversight on dose or compliance to correct intervals etc. As a result, complex antimalarial regimens are particularly problematic</td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td>SP, piperaquine, mefloquine, amodiaquine and their metabolites</td>
<td>Artemisinin-combination anti-malarials are currently being introduced in several countries</td>
<td>Yes - for amodiaquine with chloroquine and some evidence for mefloquine and lumefantrine – possibly even artemisinins</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Short-half life of artemisinin partner drugs a concern in areas of high transmission</td>
<td></td>
<td></td>
<td>This is tough to find evidence for, except at the extreme, given that such a high fraction of antimalarials are taken with absolutely no oversight on dose or compliance to correct intervals etc. As a result, complex antimalarial regimens are particularly problematic</td>
<td></td>
</tr>
<tr>
<td>Shigella</td>
<td></td>
<td>Within drug class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholera</td>
<td></td>
<td>Within drug class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td></td>
<td>High (at least) in industrialized countries</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For example, one study in Australia found that 91% (n=33) of isolates resistant to Rifampin were also resistant to Isoniazid (another key first-line drug): http://cat.inist.fr/?aModele=afficheN&cpsidt=1229895

Whereas mono-resistance to isoniazid is quite common, mono-resistance to rifampin is rare.” See, for example, http://respiratory-research.com/content/2/3/164

“...The association between community-wide use of antibiotics and the emergence of pneumococcal resistance has been demonstrated for B-lactams, macrolides and fluoroquinolones...recent antibiotic use has been shown repeatedly to be the strongest factor for the carriage and spread of resistant pneumococci, at both the individual and community levels” (Klugman KP. Antibiotic selection of multiply resistant pneumococci. Clin Infect Dis 2001; 33:489–91. Dowell SF, Schwartz B. Resistant pneumococci: protecting patients through judicious use of antibiotics. Am Fam Physician 1997; 55: 1647–8 cited in Nuernberger EL and WR Bishai. Antibiotic resistance in Streptococcus pneumoniae: what does the future hold? Clinical Infectious Diseases 2004; 38(Suppl 4):S363-71
Health system factors that drive resistance

A wide range of health system factors influence patient, provider and community behavior, resulting in actions that can drive resistance. Diagnostic and treatment services may be lacking or of poor quality; health staff may not be present when they are supposed to be (due to an under-supply of trained staff or due to trained staff having migrated to other countries or practicing instead in private facilities), or they may treat patients adversely (due to being overworked and/or underpaid); drug stock-outs may be frequent or available drugs may have expired. Available unexpired drugs may also simply deteriorate due to inadequate storage conditions (for example hot, humid conditions for drugs which are supposed to be kept in dry, cooler environments). All of these factors can motivate or demotivate patients and providers to act in certain ways that can result in inappropriate (both under and over) use of medicines. This section outlines some of the key health system weaknesses identified in the literature that contribute to drug resistance driving behavior; the behavioral factors are addressed in greater detail in the following section.

Lack of services, (direct and indirect) cost of services and poor quality services

By “services,” we mean the actual physical health facility infrastructure, alongside the human and drug and other supply (such as diagnostic tools) components which are critical inputs of an effective system. Health facilities may be few and far between, resulting in considerable direct and indirect access costs for the patient. A patient may need to seek care (or pick up drugs) on a regular basis (as in the case of ART); in this case the direct – of transport and, sometimes, clinic - and indirect – e.g. time off work - costs may deter regular pick-ups and result in irregular or interrupted treatment. Along the same lines, if a patient must report to a TB DOTS facility on a regular basis so that treatment is observed, the costs of this time may be too dear and cause the patient to default on treatment. This can be offset to some extent by
programs that bring the drugs to the patient, rather than vice versa. Even for acute conditions, having to return to pick up medicines may inhibit patients from completing a full course of treatment; for example in Indian Government hospitals patients are usually given medicines for only three days of a 5 or 7 day course of antibiotics; as a result, patients rarely return as most are daily wage earners and cannot afford to lose this income.

Direct drug costs may be beyond patient financial reach; for example, in one African country struck by conflict, up to 75% of the population were not able to afford a full CQ treatment course from either the official public health authorities or the private sector – under such circumstances it is common to delay treatment, purchase an incomplete course or share medicines – with the resulting consequences of treatment failure and selection of drug resistant strains. Additional evidence from Sub-Saharan Africa shows how cost impedes treatment: one review of 32 publications reporting on 33 patient cohorts found ART program retention rates to be about 60% at the end of the second year of treatment; the 40% who were lost to follow up often had died, but, in several cases, they had simply dropped out, possibly due to high costs of transport or clinic fees. Indeed, there is evidence from Malawi that 24% of patients who were classified as “lost to follow up” returned to the same clinic two years later when ART became free of charge.

Public sector services may have a reputation of being of poor quality, due to drug unavailability (resulting from regular interruptions to the drug supply chain) or drug leakage (theft, diversion), lack of staff to evaluate, prescribe and dispense and/or due to staff attitudes (resulting from them being overworked, overstretched and unmotivated by the frustrating combination of lack of drugs and overwhelming need). Additionally, waiting times are often extremely long, implying additional costs for the patient. To compound the problem, patients are often referred to services that are even further away. All these factors can drive patients to the formal private sector, where, while they may have to pay a fee, waiting times tend to be shorter. Alternatively they may resort to the informal private sector, purchasing (often substandard or counterfeit – see box 3 below) drugs from the vast amount of drug sellers found throughout the developing world. This is cause for concern, especially as unrestricted antimicrobial drug access may well be the most favorable predisposing situation for resistance development.

A collapse in health systems clearly can drive resistance, as can be seen through the example of MDR-TB in the former Soviet Union where, following decades of TB prevalence decline, the overwhelming

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[151] Several community-based TB programs function on this principle and have been quite successful in retaining patients on treatment through to treatment completion.

[152] Around the world a wide variety of innovative incentives and enablers have been used to offset the direct and indirect costs incurred by the patient for different diseases, some with considerable success. For a review of how these have been used in TB control, see, for example, A. Beith, R. Eichler and D. Weil. Performance-based incentives for health: a way to improve TB case detection and treatment completion? CGD Working Paper #122. April 2007. Available online at www.cgdev.org/files/13544_file_TB_final.pdf.

[153] The WHO / Health Action International surveys have a wealth of data on drug affordability (see http://www.haiweb.org/medicineprices/)

[154] Drug diversion is linked to resistance because it results in quality antimicrobials being taken out of a regulated health system which increases the drug supply in the unofficial sector, where misuse is common and drugs may be more likely to degrade due to improper storage. It also makes it likely that official health systems will replace the lost drugs with medicines procured from dubious sources. Alternatively, the patient who faces an ‘out of stock syndrome’ is forced to procure the drug from a less assured provider (Iruka Okeke, personal communication).

[155] In the case of ART, there is also evidence that, when drugs are not available, providers may choose to switch regimens to maintain patients on treatment and that the source of these drugs often is either the private sector or drug donations from family members abroad – clearly not a rational method of drug use (Sebulime G, Muyingo S, Sebbale K, Nicole J, Robinson JN, Kabugo C. Access to laboratory monitoring and HIV-antiretroviral use in the private-for-profit sector in Uganda [abstract MoOrB1097]. Proceedings of the 14th International AIDS conference, 7-12 July 2002, Barcelona).
changes to the society as a whole (comprising the collapse of public health infrastructure, TB drug
supply problems, transmission within institutions (primarily prisons) and a dramatic decrease in
socioeconomic conditions) contributed to spectacular increases in TB, MDR-TB\textsuperscript{156} and XDR-TB\textsuperscript{157}.
Recent increases in MDR-TB in Peru are also hypothesized to be at least partially due to a general health
system collapse during 2003-2004\textsuperscript{158}. Indeed analysis by members of the WHO/IUATLD Global
Project on Anti-tuberculosis Drug Resistance Surveillance notes that “geographical areas with a high
prevalence of multidrug resistance have a history of poor tuberculosis control and widespread and
uncontrolled use of anti-tuberculosis agents”\textsuperscript{159}. Inadequate TB case and program management, leading
to widespread poor adherence and treatment failure, have been argued to be the key drivers of MDR-
TB\textsuperscript{160}.

\begin{boxedminipage}{\textwidth}
\textbf{Box 3: The problem of substandard medicines (including counterfeit)}

According to the WHO, up to 25\% of all medicines in the developing world are counterfeit. Counterfeit
drugs containing no active ingredient, while clearly not helping the patient, do not drive resistance.
However drugs which contain sub-clinical amounts of the active ingredient, or those that contain a less
absorbable form of the drug or formulation, or those that are expired and relabeled (and thus almost
certainly do not contain the required clinical dose) can be huge drivers of resistance. For example, a
devastating counterfeit would be a fixed combination anti-malarial with half the artemisinin and none of
the second combination drug.

Sub-therapeutic levels of antimicrobial agents result not only from consumption of low dosage
counterfeit drugs, but also from poor adherence to correct dosage medicines and deterioration of
drugs\textsuperscript{bbb} due to poor transport and storage conditions (this issue is further addressed later in the paper).
Other drug quality issues that can arise for correct dosage drugs that incur transport and/or storage
challenges or for counterfeit drugs include dissolution: i.e., if a tablet or capsule does not dissolve
properly, the active ingredient will not be released into the blood stream. Additionally, if a product if
past the expiration date, it may degrade to the extent that it is no longer effective.

Some country-specific data on counterfeit/substandard drugs include:

\begin{itemize}
\item It is estimated that, in Nigeria and Pakistan, between 40-50\% of all drugs are counterfeit, while this
percentage for some products in China is between 50-85\%.
\item A 2008 study\textsuperscript{161} of the quality of antimalarials in six Africa countries found that 35\% of all samples
were substandard, while 33\% of treatments were artemisinin monotherapy (which is directly counter
to policy advocated by WHO).
\item In Thailand and Nigeria 36.5\% of antimalarials on the WHO EDL are substandard.
\item A recent WHO survey of seven African countries found that between 20-90\% of antimalarials failed
quality testing (failure for CQ was from 23-38\% and up to 90\% for SP tablets).
\item Recent surveys suggest that 38-53\% of shop-bought artesunate in mainland South-East Asia are fake
– these have been found in Burma, on the Thai/Burma border, in Cambodia, Laos, Vietnam and the
Peoples Republic of China.
\item Global fund grantees have three options to procure ARVs (through a) FDA/EMEA; b) WHO
prequalification; or c) products not reviewed by a regulatory authority). According to a February
2007 Global Fund report, of 2,254 single or limited source products procured, one-fifth were
purchased using option (c) and half of these ARV option (c) purchases were found to be non-
compliant to the quality assurance policy. Additionally, notification is required when countries use
\end{itemize}

\textsuperscript{bbb} Antibiotics are particularly susceptible to this, especially antimalarials (Iruka Okeke, personal communication)
option (c) so that random quality testing can be undertaken on non-approved products. However the Global Fund was notified of the option (c) purchase in only 2 of 426 cases. The quality of many ARVs procured therefore is questionable.

It can be argued that the greatest deterrent to counterfeiting is a reliable supply of good quality, low cost drug products.

Lack of or weak implementation of regulations governing prescribing and dispensing

Many, if not most, developing countries do not regulate prescribing and dispensing behavior. Even in countries where standard treatment guidelines (STGs) have been developed, these tend to be poorly implemented. Strategies that have increased the use of guidelines and have had a resulting impact on antimicrobial prescribing practice include active guideline dissemination, local involvement and provision of feedback to prescribers. STGs are rarely taken into consideration by the private sector; and formal arrangements/agreements between public authorities and private providers are rare. However there are some notable exceptions (see Box 4 below).

Promotion of rational drug use is poorly integrated into health systems and, alongside resistance, should be more rigorously included in medical student, health worker and pharmacist curricula. Professional bodies have a role here as well as they act as providers of continuing professional development, advice and guidance, and can have a regulatory/quality assurance aspect to their work. Thus, at the global level, it is worth considering how the umbrella professional associations (e.g. FIP for pharmacists) can influence rational selection and use with a view to tackling drug resistance.

Changes in overall government policy influence how drugs are prescribed and dispensed and by whom. In Vietnam in 1986, economic reforms privatized many sectors, including drug provision. As a result, in the absence of prescribing and dispensing regulations, individuals widely began to treat themselves, easily buying antibiotics without a prescription. There is evidence that up to 90% of drug dispensing was without a prescription and that 94.9% of individuals themselves chose which drugs to buy.

National-level campaigns in both Finland and Iceland targeting both providers and the general public have been effective at decreasing antibiotic prescribing and use and have been associated with declines in \textit{S. pneumoniae} resistance. Campaigns have been shown to be more effective if repeated regularly and when interventions targeting patients are accompanied by provider education efforts.

**Box 4: Collaboration between public and private sectors to slow resistance**

Stop TB’s public-private mix initiative (PPM) has given rise to many examples of how private doctors can be supported to follow government STGs for TB and how it has been documented that this collaboration leads to improved treatment outcomes and indirectly prevents MDR-TB.

Guidance on

\textsuperscript{ccc} Two interesting points should be highlighted here: first that it took two years from implementation of the national guidelines for any impact to be shown and secondly that resistance decreased to macrolides and trimethoprim-sulfamethoxazole but not to beta-lactams, a finding which “reveals the potential for cross-selection of resistance by different antibiotic classes and reinforces the importance of reducing the use of all antibiotics, not just selected classes” (Nuernberger EL and WR Bishai. \textit{Antibiotic resistance in \textit{Streptococcus pneumoniae}: what does the future hold?} \textit{Clinical Infectious Diseases 2004; 38(Suppl 4):S363-71})

how to plan and implement PPM approaches is available at http://www.who.int/tb/careproviders/ppm/en/

The International Standard of TB Care (ISTC) (http://www.who.int/tb/publications/2006/istc/en/) is an important tool for PPM implementation. The ISTC has been developed and endorsed by many international technical partners and professional association in several countries. It is a document that may be easier to accept by private providers because it is not a government decree, but a document that speaks the language of the clinicians and the professional associations. However, the messages, the standards, are the same as the WHO guidelines on TB diagnosis, treatment and management.

Over the past decade, several countries have mounted successful efforts to decrease the number of antimicrobial prescriptions and/or the total volume of antimicrobial use (see table 13 below). Evidence from Chile, for example, shows how effective enforcement of laws restricting antimicrobial purchase only to those who have a prescription can have a sustained impact within the outpatient setting; sales fell by 43% from US $45.8 million in 1998 to US $26.1 million in 2002.169

**Table 13: Countries that have decreased either number of antimicrobial drug prescriptions or total volume of outpatient antimicrobial drugs used within the last 10 years**170

<table>
<thead>
<tr>
<th>Continent</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>Belgium, France, Germany, Spain, Sweden and the United Kingdom</td>
</tr>
<tr>
<td>Asian-Pacific region</td>
<td>Australia, South Korea, Taiwan</td>
</tr>
<tr>
<td>Americas</td>
<td>Canada, Chile and the United States</td>
</tr>
</tbody>
</table>

In contrast to industrialized nations, the need in developing countries is to achieve more appropriate prescribing and use (and actually increasing total volume, rather than decreasing total use)171.

**Lack of education and training among dispensers accompanied by poor monitoring and enforcement**

In many countries, even formal drug dispensers in both the public and private sectors are poorly trained or not trained at all. To add to this, there is often little to no monitoring of dispensing behavior or follow-up to change inappropriate behavior. Global estimates suggest that over 50% of antibiotics are dispensed without a prescription, often by informal providers who have little to no training172.

**Lack of or weak implementation of infection control policies**

Effective infection control is lacking in many, if not most, developing countries. Poor infection control is a glaring driver of infection and resistance transmission, especially in the in-patient environment (i.e. hospital acquired infections (HAI)), but also in the community173. Substandard infection control policies and implementation clearly drive resistance transmission. Indeed, while selection pressure drives resistance emergence, the main driver of transmission in the health care setting has been argued to be inconsistent application of infection control policies174. Evidence from Estonian, Russian and Georgian hospitals and prisons shows how poor infection control measures have led to high rates of MDR-TB transmission among patients, staff and inmates175. Additionally, rural South Africa’s recent MDR-TB

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**Investigation of drug-resistant strains from the hospital to the community is a great cause for concern.** Previous hospitalization often is a significant risk factor for the acquisition of a resistant infection in family members. (Zaidi, M. B., E. Zamora, P. Diaz, L. Tollefson, P. J. Fedorka-Cray, and M. L. Headrick. 2003. “Risk Factors for Fecal Quinolone-Resistant Escherichia Coli in Mexican Children.” Antimicrobial Agents and Chemotherapy 47 (6): 1999–2001. This can be due to the hospitalized individual bringing the strain home or the family member acquiring the strain while caring for the individual while in hospital. Weak health systems in developing countries often mean that family members spend much time in the clinical setting with the ill individual, providing comfort and care as possible, alongside food and other material supplies from home.
and XDR-TB outbreak suggests that both nosocomial and community transmission of MDR-TB and XDR-TB took place. In the South African case, poor infection control measures clearly played a role in transmitting TB which, in this case, included considerable amounts of drug-resistant TB. Previous hospitalization has been shown to be a strong risk factor for MDR-TB and XDR-TB, in particular where infection control is weak and where there is a high prevalence of HIV positive individuals.

Lack of high-quality highly-accurate rapid diagnostic tools

In many developing countries there is poor to no access to high-quality highly-accurate rapid diagnostic tools (RDTs). The lack of a clear diagnosis can result in widespread drug overuse, causing drug selection pressure and leading to greater resistance (as is the case of malaria where many patients presenting with febrile illness, in the absence of a clear diagnosis, are treated for malaria). If higher quality rapid diagnostic tests existed and were accessible to the populations that require them, it is assumed that drug overuse and misuse would decline.

As the situation stands, an uncertain diagnosis may lead health providers towards recommending that treatment be started at a low threshold. This particularly occurs in low malaria transmission settings where a positive test almost certainly means that the illness is malaria. It also occurs for infections where the provider is not certain about whether the cause is bacterial or viral, in which case an antibiotic (often broad-spectrum) may be prescribed for what instead is a viral infection, in turn leading to selective pressure on endogenous flora.

Paucity or poor quality of resistance surveillance efforts

No matter the disease, few developing countries or regions have traditionally undertaken systematic surveillance of drug resistance. The need for and degree of individual patient testing for resistant strains (to ensure that a treatment naïve patient does not carry an already resistant strain prior to initiating treatment) is a debate that differs by disease and resources available. For example, in developed countries, guidelines usually recommend testing of recently infected HIV positive individuals for resistant strains, but do not generally recommend testing for chronically infected individuals, primarily due to a lack of data to support testing and a lack of information about rates of viral resistance among chronically infected individuals. However recent evidence points to a persistence of drug resistance mutations in chronically HIV-infected patients and an increasing prevalence of resistance over time; findings that support genotyping of virus at baseline for chronically HIV-infected patients, hardly a realistic option in developing countries. As a TB example reveals, even where drug sensitivity testing is used, as the required laboratory infrastructure exists and local policy supports using it, time lags may mean that patients die before results from drug resistance testing become available.

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**iii** An additional challenge is the lack of lab capacity. If new rapid diagnostic tests can overcome the need for microbiological diagnostic tests then that may become less of a problem – but for now the answer is stronger microbiology! This is a health system infrastructure and human resource issue.

**ii** However there is evidence that there is more to decision-making than a rapid diagnosis: even when accurate rapid diagnostic tests exist and are used, providers may continue to provide drugs, even when not warranted, for a number of behavioral reasons addressed in the following section. See, for example, H Reyburn, R Mbatia, C Drakeley, I Carneiro, E Mwakasungula, O Mwerinde, K Saganda, J Shao, A Kitua, R Olomi, BM Greenwood and CJM Whitty. Over-diagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. BMJ 2004;329;1212

**iii** This does not hold true in higher malaria transmission areas, where the prevalence of asymptomatic malaria parasitaemia is high, and a positive test does not mean the patient has malaria (Nicholas White, personal communication)

**iii** For example, in one study “conducted in Tugela Ferry, South Africa, the median duration of survival from the time of collection of sputum samples for culture and DST was just 22 days for patients with MDR-TB and 14 days for patients with XDR-TB; both periods are much shorter than the period required for conventional culture and DST results to
Where they are ongoing, surveillance efforts can bump up against classification problems. In the case of *Shigella* for example, specific confounding comes from amoebic dysentery (treated with a different repertoire of drugs e.g. metronidazole), enterohemorhagic *E. coli* infection (where antimicrobials should not be used) and some viral infections (where antimicrobials would not help)\(^{182}\). All these conditions present with identical symptoms and signs. Additionally, routine recording usually classifies bloody diarrhea together with watery diarrhea which, given the fact that ORT introduction and use has caused decreases in watery diarrhea in the recent past, may result in a perceived reduction of *Shigella* (which is unlikely, as ORT has a limited impact on *Shigella*)\(^{183}\).

In recent years national, regional and global surveillance efforts to capture absolute levels and trends in drug resistance have been stepped up. Examples include the WHO/IUATLD global project on drug resistance surveillance which was created in 1994 and produces periodic reports\(^{iii}\) on global levels of and, where possible, trends in anti-TB drug resistance. However, despite this, the true magnitude of the MDR- and XDR-TB problem in Africa (the region with the highest TB incidence in the world) remains unclear (due to severely limited laboratory capacity, lack of appropriate equipment and trained personnel)\(^{184}\). For malaria, there is interest in developing an international database on drug resistance information (primarily levels and trends)\(^{185}\). Box 5 below describes current efforts in ART-resistance surveillance globally.

**Box 5: Ongoing global ART resistance surveillance efforts**

The WHO’s recently-established HIVDR Global Laboratory Strategy aims to “support national, regional, and global HIVDR surveillance and monitoring by the timely provision of quality assured genotyping results in a standardized format that meets WHO specifications”\(^{186}\). This strategy is being taken forward by a network of national, regional and specialized labs. Each country can choose to have specimens genotyped in a WHO accredited regional or specialized laboratory or to perform this function themselves within their national laboratory. Regional labs are meant to support HIVDR surveillance and monitoring efforts in their region; there is supposed to be at least one per WHO region. In addition to providing genotyping services to countries in their region that do not have WHO-accredited national laboratories, these labs also provide technical assistance and training. Specialized laboratories, for their part, are designed to assist in the implementation of Quality Assurance Programs, provide capacity building and training, perform operational research and carry out HIVDR testing for some of the countries without an accredited laboratory for DFS (dried fluid spot) technology development.

To date, 32 labs have been assessed for accreditation, while seven have been accredited so far, of which 4 are specialized labs (Utrecht (Netherlands), Montpellier (France), Madrid (Spain), Ottawa (Canada)), two are regional labs (Melbourne (Australia), Martinique (Caribbean)) and one is a national lab. (Pune, India). Developing country labs currently undergoing assessment for accreditation are based in the following cities:

- in Africa: Dakar, Kampala, Nairobi (4 labs), Johannesburg (2 labs)
- in Asia: Jakarta, New Delhi, Chennai, Kolkata, Beijing (2 labs), Shanghai and ShenYang

WHO also recommends that countries monitor seven different ART site-level program factors (called HIV Drug Resistance Early Warning indicators - EWIIs) which are associated with preventing drug resistance; indicator monitoring, in conjunction with surveillance data, can help guide action to slow
resistance development\textsuperscript{187}. These seven indicators address ART prescribing practice, patients lost to follow-up during the first 12 months of ART, patient retention on first-line ART at 12 months, on-time ARV drug pick-up, ART clinic appointment-keeping, pill count or adherence measure using a standard instrument and drug supply continuity\textsuperscript{188}. As of June 2008, countries piloting the EWIIs included Cambodia, China, Ethiopia, Ghana, India, Indonesia, Malawi, Swaziland, Uganda, Vietnam, Zambia and Zimbabwe\textsuperscript{189},\textsuperscript{kkk}. Of these countries, only Malawi had completed their pilot. Many additional countries have included EWI monitoring in their plans, but have not begun piloting yet\textsuperscript{190}.

The global community currently lacks the systems to quantify global resistance in terms of morbidity and mortality. There is urgent need for work in this area to be able to show the true extent of the problem; for example, it has been suggested that death reporting requirements include whether the pathogen that caused the patient’s death was resistant to the antibiotic therapy given or not\textsuperscript{191}.

The two tables below aim to compare health system factors across diseases. The first, Table 14, looks at organizational factors, while the second, Table 15, seeks to compare health system resistance drivers.

### Table 14: Comparison of some health systems organizational factors across diseases

<table>
<thead>
<tr>
<th></th>
<th>How is the disease program usually run?</th>
<th>Where are drugs primarily accessed?</th>
<th>What is the most common setting for diagnosis?</th>
<th>What is the most common diagnosis method/mechanism?</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Vertically</td>
<td>Public sector – hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB</td>
<td>Vertically</td>
<td>Public sector, but in some parts of the world, formal and informal private sectors (formal in collaboration with NTPs)</td>
<td>TB/PHC clinic</td>
<td>Microscopic examination of stained sputum smeared on a glass slide</td>
</tr>
<tr>
<td>Malaria</td>
<td>Vertically, yet less so than HIV or TB. PHC-oriented IMCI strategies are also important</td>
<td>Self purchase from private formal or informal used to be the case; now, with ACT FDCs, more through the public sector</td>
<td></td>
<td>Self</td>
</tr>
<tr>
<td>Shigella</td>
<td>Horizontally, as part of PHC or informally through self-medication. Outbreaks, when identified, may be managed as a public health emergency</td>
<td>Public health clinics or self-purchase</td>
<td>PHC/self</td>
<td>Clinical diagnosis is most common but extremely problematic</td>
</tr>
<tr>
<td><em>V. cholerae</em></td>
<td>Horizontally, as part of PHC or vertically as part of emergency</td>
<td></td>
<td></td>
<td>Often clinical but this is usually not problematic because typical cholera presents with a rice-water type stool that is almost diagnostic. People who present with a milder disease are probably immune from previous infection. Laboratory confirmation is needed to report outbreaks but cholera diagnosis can be reasonably reliably made clinically</td>
</tr>
<tr>
<td><em>S. pneumonia</em></td>
<td>Horizontally, as part of PHC</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{kkk} For preliminary findings from these pilot studies, see [http://www.intmedpress.com/Journal%20Management/msArticleList.cfm?viewinfo=28451C267827515D43173A0B42 025003387827515752620C0D551F5F02054401252149004F3D44154405395F30190727440B27654B014A1C5E161E0B 155D3D17511379286B00453A0A1844040B68320D5A6417251E00110C58](http://www.intmedpress.com/Journal%20Management/msArticleList.cfm?viewinfo=28451C267827515D43173A0B42 025003387827515752620C0D551F5F02054401252149004F3D44154405395F30190727440B27654B014A1C5E161E0B 155D3D17511379286B00453A0A1844040B68320D5A6417251E00110C58)
<table>
<thead>
<tr>
<th>Disease</th>
<th>Lack of services, cost of services, poor quality services</th>
<th>Lack of or weak implementation of regulations governing prescribing/dispensing</th>
<th>Lack of or weakly implemented inpatient infection control</th>
<th>Lack of high quality, highly accurate rapid diagnostic tools</th>
<th>Paucity/poor quality resistance surveillance efforts</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Until recently lack was enormous; past decade has seen significant improvement</td>
<td>Of increasing importance, as ART availability and counterfeits increase</td>
<td>Not relevant, except for blood hygiene measures</td>
<td></td>
<td>International efforts underway</td>
</tr>
<tr>
<td></td>
<td>Even where ART is free, costs can be considerable (direct such as transport; indirect for time off work)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB</td>
<td>Lack and poor quality can be an issue; cost, in theory, should not be as TB treatment should be provided for free. However, as with ART, TB treatment implies direct and indirect costs, which can be considerable, give the length of the treatment</td>
<td>Increased involvement of the private sector in TB treatment in several Asian countries has proven quite successful</td>
<td>Only an issue in settings where the treatment initiation phase (first two months) takes place in an in-patient setting</td>
<td></td>
<td>Major efforts made over past 10 years</td>
</tr>
<tr>
<td>Malaria</td>
<td>All may be factors contributing to self-medication</td>
<td>Of crucial importance, given the amount of overmedication and substandard medicine availability have been reported</td>
<td>Only an issue for patients who are admitted to hospital for malaria or another reason</td>
<td>Of crucial importance given the amount of overmedication that has been reported (though providers may continue to provide antimalarials when a test comes back negative – see next section on behavior)</td>
<td>Several regional initiatives; effort underway to create a global malaria resistance database</td>
</tr>
<tr>
<td>Shigella</td>
<td>All may be factors contributing to self-medication</td>
<td>Substandard medicines</td>
<td>A critical issue</td>
<td>Of crucial importance</td>
<td>Management of both <em>Vibrio cholerae</em> and <em>Shigella</em> infections is compromised by poor surveillance because therapy must begin empirically and because there are considerable temporal and geographical variations in resistance profiles192,193</td>
</tr>
<tr>
<td>Cholera</td>
<td>All may be factors contributing to self-medication</td>
<td>Of crucial importance, as antibiotic not warranted outside of an epidemic setting</td>
<td></td>
<td></td>
<td>Less important than <em>Shigella</em></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>All may be factors contributing to self-medication</td>
<td>Substandard medicines</td>
<td>A critical issue</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Behavioral factors that drive resistance

There are many patient, provider and community behavioral factors that drive resistance. These often derive from “misaligned incentives,” where the incentives driving patient and/or provider do not align with those of a hypothetical social planner’s optimal set of choices. This misalignment can lead to inappropriate stocking, prescribing and use. An understanding of what motivates people, both hypothetically and in practice, is crucial in order that appropriate behavior change interventions can be designed and implemented.
What are common factors that motivate patient behavior?

Poor adherence plays a critical role in driving resistance; factors that can complicate adherence include length of treatment, drug side effects, or, on the contrary, when the patient feels better and discontinues medication before the course is completed. For chronic life-long treatment, such as ART, many factors have been identified to affect adherence levels (see Table 16 below); these factors often play a role in other conditions that require a long course of treatment, such as TB. There also is evidence that ART drug-sharing can result in poor treatment adherence.

Table 16: Factors reported to affect adherence to therapy among HIV-infected patients

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Medication factors</th>
<th>System of care factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active substance abuse (drugs and/or alcohol)</td>
<td>Dose frequency of &gt;2 per day</td>
<td>Dissatisfaction with past experience of health care system</td>
</tr>
<tr>
<td>Male sex</td>
<td>Pill burden</td>
<td>Poor doctor/health care provider relationship</td>
</tr>
<tr>
<td>Youth</td>
<td>Type of drug</td>
<td></td>
</tr>
<tr>
<td>Active depression</td>
<td>Inability to take medication when away from home</td>
<td></td>
</tr>
<tr>
<td>Lower level of education</td>
<td>Food requirement</td>
<td></td>
</tr>
<tr>
<td>Pain and anxiety</td>
<td>Side effects</td>
<td></td>
</tr>
<tr>
<td>No change in health status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minority race/ethnicity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Community and/or family-level stigma can play a crucial role in many societies in motivating (or demotivating) individual behavior, such as health seeking behavior. Individuals may choose to go to informal, untrained and unregulated providers or not seek any health services at all if they suspect they have a sexually- or poverty-linked disease such as HIV or TB. Stigma can lead to discrimination which, in turn, may lead to poor referral practices: for example HIV positive patients (in particular homosexual men or intravenous drug users) may be viewed as “to blame” for their condition and not promptly referred by health providers (for TB diagnosis and treatment for example).

Sometimes a patient has the incentive to self-medicate. For example, malaria drugs are easy to come by in many countries, even those requiring prescription, and patients may be motivated to purchase them directly without a formal diagnosis. However drugs purchased may be substandard or self-diagnosis may be incorrect so use ends up being inappropriate.

The cost and accessibility of a fragmented drug regimen (purchasing less than a full-course or even one dose at a time) is sometimes more feasible to the patient than purchasing a complete regimen. When medicines are sold per tablet/per capsule/per milliliter at lower cost than purchasing the complete regimen, there is an obvious financial incentive to purchase only what the patient considers essential.

In many parts of the world, cultural preferences and beliefs (such as higher effectiveness of multi-colored capsules over plain ones or injectables vs. pills) also can have a large impact on individual behavior. Socio-cultural factors definitely play a role in community-level medicine whether the community is urban, rural or peri-urban. Local leaders and their role in defining culture and habits

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It is important to note, however, that obtaining drugs from the official sector does not guarantee their quality. Because procurement may be leaky, poor quality drugs can and have been found in hospitals and pharmacies as well as from unofficial drug sellers (Iruka Okeke, personal communication. See for example: Okeke, I. N., and A. Lamikanra. 1995. Quality and bioavailability of tetracycline capsules in a Nigerian semi-urban community. International Journal of Antimicrobial Agents 5:245-250 and Taylor, R. B., O. Shakoor, R. H. Behrens, M. Everard, A. S. Low, J. Wangboonskul, R. G. Reid, and J. A. Kolawole. 2001. Pharmacopoeial quality of drugs supplied by Nigerian pharmacies. Lancet 357:1933-6).
can play a determining role in patient adherence; for example, in one study from India, 50% of HIV positive patients who were referred to specialist centers as they were not responding to treatment had stopped taking ART on the recommendation of a traditional healer\textsuperscript{202}.

Gender-related issues may also play a role in behavior. For example, in some societies it is inappropriate for a woman to travel unaccompanied by a male. Therefore frequent trips to a health clinic might prove problematic. Another example is that, when women in India are given ART, they often take it home and share it with their husbands and children\textsuperscript{203}. The lesson here is that the HIV positive family must be treated as a unit, ensuring that all members are on ART\textsuperscript{204}.

*What are common factors that motivate provider behavior?*

As mentioned in the previous section, where diagnosis is uncertain, there is a tendency for providers to overtreat. Even when diagnostic tools reveal a negative diagnosis, clinicians sometimes do not trust this result (or their perception that the patient desires or needs the medicine outweighs the test result) and the drug is provided despite the counter indicated test result. In Tanzania, one study found that, in low-moderate malaria transmission settings, more than 90% of antimalarial prescriptions were for patients for whom a test requested by a provider came back negative for malaria\textsuperscript{205}. What is more curious is another study by several of the same authors in Tanzania, showing that in 66% of the cases when malaria parasite slides came back negative for a severely febrile patient, clinicians did not choose to treat the infection with antibiotics (even if this were to be in addition to an antimalarial)\textsuperscript{206}. This example reveals the extent to which it is critical to understand what factors motivate and drive behavior at the local level, and to address them through behavioral incentive changes, and not just through technology. There is a clear need for reliable and credible diagnostic measure and supportive flow charts and algorithms to help assist the provider in making as evidence-based a decision as possible about whether to treat or not and, if so, with what\textsuperscript{207}. Such guidelines would also assist the provider in convincing the patient of the most appropriate measure to take (again treatment vs. no treatment and, if the former, with what, and for how long). In the absence of these two key tools (effective and accurate diagnostic measures and supportive algorithms) providers are motivated to prescribe a broad-spectrum antibiotic, rather than a narrow-one\textsuperscript{207}, or an anti-malarial instead of an antibiotic.

Financial opportunities within the patient-prescriber-dispenser interaction also motivate behavior. Is the provider also the drug dispenser, for example? The provider who makes a profit from drug sales (or just from the consultation that accompanies a drug hand-out) has the incentive to make a “transaction.” In countries where the provider also dispenses the drugs, there are strong incentives to overprescribe or prescribe new and expensive broad-spectrum antibiotics\textsuperscript{208}. Providers in many Asian countries, for example, often receive a good part of their income from drug sales, in particular broad-spectrum antimicrobials\textsuperscript{209}, rather than from services charges\textsuperscript{209}. Their incentive therefore is to compensate for low service fees by overprescribing. In China, recent health sector reforms have resulted in 100,000 public hospitals being allowed to generate revenue from drugs sold\textsuperscript{209}.

\textsuperscript{201} Indeed, both physicians and patients often feel overwhelmed with the complexity of clinical information on infectious diseases and available therapies (Outterson K. The Vanishing Public Domain: Antibiotic resistance, pharmaceutical innovation and intellectual property law.)

\textsuperscript{202} However effective policy measures can address this challenge; for example, in Korea enforced regulation no longer allowing physicians to dispense drugs and pharmacists from prescribing decreased overall prescribing levels and levels of prescribing of antibiotics for viral infections (Park S, SB Soumerai, AS Adams, JA Finkelstein, S Jang and D Ross-Degnan. Antibiotic use following a Korean national policy to prohibit medication dispensing by physicians. *Health Policy and Planning*, July 2005, pp).

\textsuperscript{203} It is important to recognize how financial (and other) incentives can be “re-worked” to promote resistance-slowing measures. For example, in the United States, Medicare is moving towards refusing to pay for hospital acquired infections, which clearly motivates the hospitals to ensure that high quality infection control procedures are in place and effectively implemented (K. Outterson, personal communication)
In some contexts, pharmaceutical attempts to influence prescribing behavior can be fierce. For example, promotional leaflets from one pharmaceutical company in India indicate the use of rifabutin for MDR-TB, which is neither in line with the recommendations of the Indian public TB authorities nor with international guidelines. Additionally, again in India, pictures on one company’s rifabutin product drug box suggest that rifabutin can be used for MDR-TB treatment, while the insert only talks about its use in advanced HIV disease. There is also evidence of drug-industry sponsored workshops during which practitioners come up with guidelines that contradict both Indian and WHO TB control program policies and guidelines. In 2008, India’s NTP is considered very strong at both the national and state levels – a survey from the state of Gujarat reports relatively low MDRTB rates (around 2.3%). While this figure does not capture the (quite substantial amount of) TB patients being treated in the private sector, most re-treatment public sector MDR patients are coming from the private sector, a further indication that private sector prescribing is possibly not in line with Government of India (GOI) recommendations.

What factors might motivate behaviors during the patient-provider interaction?

Providers often assume that a patient desires a drug (which, indeed, often is the case) and, therefore, choose to “satisfy the customer,” on the principle that this leads to a better relationship and more chance the patient will return when a new illness or episode occurs. This assumption may also be a reason behind providers providing a drug when diagnostic tests come back negative.

Prescribing a drug also provides a psychological signal that the consultation is over; a transaction has taken place whereby the patient has received something tangible for his costs (direct in terms of payment for services, indirect in terms of time and travel cost) and the physician can move on to the next patient at his or her discretion.

Another critical issue in the patient/provider interaction is whether providers take the time to ask patients about their drug use and, if so, when it is poor, whether they try to influence patient behavior. For example, when a patient shows up who is clearly failing 1st line ART, a provider is bordering on negligence if s/he does not determine whether the treatment failure is due to poor adherence. In the case that it is, prescribing more costly and complex second-line treatment may be irresponsible, if the patient does not adhere any better to the treatment course.

Industry also plays a role in influencing patient behavior. As touched upon above, the pharmaceutical industry advertises heavily not only to prescribers and dispensers, but also directly to consumers. Advertising may make the consumer feel he/she has some knowledge about the drug product and may prompt/empower him or her to suggest the particular drug to the prescriber. The extent to which industry advertising motivates prescribing behavior and consumer input to prescribing behavior has not been quantified in developing country settings, but is suspected to be considerable.

There is also some evidence of unpleasant health worker behavior contributing to increased patient treatment default; this can be due to heavy workloads and resulting neglect of or poor quality interactions with patients. Evidence from South Africa, for example, points to health care workers refusing to care for patients with XDR-TB, requesting reassignment or leaving their posts (Andrews, JR, Shah NS, Gandhi N, Moll T and G Friedland. Multidrug-resistant and extensively drug-resistant tuberculosis: implications for the HIV epidemic and antiretroviral therapy rollout in South Africa. Journal of Infectious Diseases 2007:196 (Suppl 3)).
ART treatment guidance about the importance of adherence and how to overcome barriers to adherence. When providers are too busy this task may go undone\textsuperscript{217}.

It could be argued that the patient/provider interaction boils down to whom do patients trust most? The provider who is available, who listens, who has time, who gives out medicines? In many circumstances a well-trained private or public community-health worker may be the most appropriate individual to assume this role and “may have greater potential for providing continuity of care and supporting treatment driven partly by the economic incentive to retain client loyalty”\textsuperscript{218}.

Table 17 below provides an overview of behavioral drivers across diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Factors that motivate / demotivate the patient</th>
<th>Factors that motivate/demotivate the provider</th>
<th>Factors that drive behavior during the patient/provider interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Adherence challenges</td>
<td>Financial gain</td>
<td>Industry pressure to prescribe certain drugs</td>
</tr>
<tr>
<td></td>
<td>Financial costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stigma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cultural preferences</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gender issues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB</td>
<td>Adherence challenges</td>
<td>Lack of supportive algorithms</td>
<td>Industry pressure to prescribe certain drugs</td>
</tr>
<tr>
<td></td>
<td>Financial costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stigma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cultural preferences</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gender issues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td>Incentive to self-medicate</td>
<td>Uncertain diagnosis</td>
<td>(Real or perceived) pressure from patient to treat</td>
</tr>
<tr>
<td></td>
<td>Financial costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shigella</td>
<td>Incentive to self-medicate</td>
<td>Uncertain diagnosis</td>
<td>(Real or perceived) pressure from patient to treat</td>
</tr>
<tr>
<td></td>
<td>Financial costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholera</td>
<td>Uncertain diagnosis</td>
<td>(Real or perceived) pressure from patient to treat</td>
<td>(Real or perceived) pressure from patient to treat</td>
</tr>
<tr>
<td></td>
<td>Lack of supportive algorithms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Incentive to self-medicate</td>
<td>Uncertain diagnosis</td>
<td>(Real or perceived) pressure from patient to treat</td>
</tr>
<tr>
<td></td>
<td>Financial costs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Elements beyond the health sector that can facilitate the driving of resistance**

Brief mention should be made of the many factors beyond the health system that can facilitate resistance (also emergence, but primarily transmission). These are mainly factors that are wide in scope and difficult for individual international donors to target with specific actions.

They include migration, civil conflict, unreliable water supply, frequency and speed of travel and international trade – in particular of food products. Malnutrition and an immunocompromised status can facilitate both acquired and transmitted drug resistance. In some parts of the world, widespread HIV is causing an increase in the number of immunocompromised patients. Situations of overcrowding and poor hygiene promote the spread of drug resistant clones that have already been selected for\textsuperscript{219}. These include urban or peri-urban slum-living conditions where many of the world’s poor live (where \textit{S dysenteriae} is common), to refugee camps (where \textit{V. Cholerae} is common), to prisons (where MDR-TB is common in Russia) to day care centers (where \textit{S pneumoniae} is common throughout the industrialized world)\textsuperscript{220}.

Animal antibiotic use also drives resistance. Antibiotics are used for growth promoting or therapeutic purposes. For the former sub-therapeutic doses are given, and that drives selection of resistant strains in animals. Resistant strains pass to humans from animals primarily through the food chain or through direct contact. The extent of this sort of transmission in developing countries is unclear as is the extent to which antibiotics are being used in these settings. The little evidence that exists points towards use
primarily for therapeutic rather than growth promoting purposes\textsuperscript{rr}. It certainly is an area that deserves more attention given that so many developing country populations live in close proximity to or even share space with animals.

Urbanization has also been linked with increased levels of resistance. For example, studies in Africa\textsuperscript{221,sss} have found \textit{E. coli} resistance levels to be higher among urban residents than rural or provincial residents. This is a particularly important issue given global trends towards rapid urbanization which seem set to accelerate rather than slow in the near-medium term. Finally, due to rising incomes, more and more people will be able to afford antibiotics, and give rise to higher levels of resistance than currently observed in some developing countries.\textsuperscript{222,ttt}

<table>
<thead>
<tr>
<th>Disease</th>
<th>Migration and conflict</th>
<th>Malnutrition and immunocompromized status</th>
<th>Overcrowding</th>
<th>Travel</th>
<th>Use of antibiotics in animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Yes (low)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>TB</td>
<td>Yes (high)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Malaria</td>
<td>Yes (low)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Shigellosa</td>
<td>Yes (high)</td>
<td>Probably</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cholera</td>
<td>Yes (high)</td>
<td>Probably</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Yes (high)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

TB/HIV disease co-infection as a possible driver of resistance

While it is clear that the HIV epidemic has led to explosive levels of TB infection\textsuperscript{www}, it is less clear to what extent HIV infection is a driver of MDR-TB prevalence. One recent review of the literature found that “the evidence for HIV infection as a specific risk factor for multidrug resistance among patients with TB is variable”\textsuperscript{223,xxx}, while the most recent (February 2008) evidence from surveys in Latvia and Donetsk, Ukraine suggest a link does exist\textsuperscript{224}. In any case, it is interesting to analyze some of the factors that might be involved when a link seems to exist. One study for example found that institutionalized outbreaks of MDR-TB in industrialized countries primarily affected HIV-infected individuals (see Table

\textsuperscript{rr} In one study in Kenya, 90\% of antibiotics were used for therapeutic purposes (see Mitema, E. S., G. M. Kikuvi, H. C. Wegener, and K. Stohr. 2001. “An Assessment of Antimicrobial Consumption in Food Producing Animals in Kenya.” \textit{Journal of Veterinary Pharmacology and Therapeutics} 24 (6): 385–90.))

\textsuperscript{sss} In Ghana, Nigeria and Zimbabwe


\textsuperscript{www} Yet \textit{M. bovis} (Bovine TB) can be transmitted from animals to humans

\textsuperscript{xxx} However there are other streptococci that infect animals – for example, the enterococci. In this case antibiotic resistance can be acquired and transmitted to humans; examples include Salmonella in cattle and Campylobacter in chickens (G. Keusch, personal communication)


\textsuperscript{xxx} Also see Andrew et al, which provides references for most of the evidence to date on this topic: (Andrews, JR, Shah NS, Gandhi N, Moll T and G Friedland. Multidrug-resistant and extensively drug-resistant tuberculosis: implications for the HIV epidemic and antiretroviral therapy rollout in South Africa. \textit{Journal of Infectious Diseases} 2007:196 (Suppl 3)).
19 below) and the consequences in terms of mortality were dramatic\textsuperscript{377}. The main drivers of this situation were determined to be: delayed diagnosis of MDR-TB (death occurred prior to MDR-TB being bacteriologically confirmed), inadequate initial treatment and prolonged infectiousness\textsuperscript{225}.

Table 19: HIV-associated multi-drug resistant tuberculosis (MDT-TB) outbreaks in industrialized countries 1988-1995\textsuperscript{226}

<table>
<thead>
<tr>
<th>Location, date [reference]</th>
<th>Patients with MDR-TB</th>
<th>Time to death, median, weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total, no.</td>
<td>HIV infected, %</td>
</tr>
<tr>
<td>Hospital (Florida), 1988–1990 [25]</td>
<td>65</td>
<td>93</td>
</tr>
<tr>
<td>Hospital (New York City), 1989–1990 [26, 27]</td>
<td>51</td>
<td>100</td>
</tr>
<tr>
<td>Hospital (New York City), 1990–1991 [27, 28]</td>
<td>70</td>
<td>95</td>
</tr>
<tr>
<td>Hospital (New York City), 1991–1992 [27, 29]</td>
<td>32</td>
<td>91</td>
</tr>
<tr>
<td>Hospital (Madrid, Spain), 1991–1995 [31]</td>
<td>48</td>
<td>100</td>
</tr>
<tr>
<td>Hospital (Buenos Aires, Argentina), 1994–1995 [32]</td>
<td>68</td>
<td>100</td>
</tr>
<tr>
<td>Prison system (New York State), 1990–1991 [33]</td>
<td>42</td>
<td>98</td>
</tr>
</tbody>
</table>

While the association between HIV-positive status and MDR-TB at the individual level is not clear, arguments can be made at the population level, namely: “the increase in the pool of immunocompromised patients who serve as both hosts and vectors for all forms of TB, including MDR-TB and XDR-TB, is certain to increase the absolute burden of drug-resistant TB at the population level”\textsuperscript{227}.

Finally, there is concern that increased use of isoniazid for preventive treatment among populations that have a high prevalence of HIV will further drive isoniazid-resistance development\textsuperscript{228}. Before IPT is initiated, active TB among HIV-positive individuals must be excluded; otherwise patients with undiagnosed TB will risk being put on isoniazid preventive monotherapy, when they should, instead, be treated with a combination of anti-TB drugs\textsuperscript{229}.

\textsuperscript{377} It should be noted that these outbreaks took place prior to the wide availability of HAART and also rapid diagnostic testing for TB drug resistance
Commonalities and differences in development of drug resistance across diseases

While some of the elements that drive resistance differ given the nature of the disease and the drugs in question, there are several commonalities across diseases. A lack of health services, costly or poor quality services can all lead to behavior, such as self-medication, that favors resistance emergence, particularly in settings where drugs are easily available and affordable through informal channels. Weak infection control is a key driver of transmission of resistant organisms (both inpatient and to the community), especially for *S. pneumoniae* and *Shigella* and, as recently seen in South Africa, MDR and XDR-TB. The lack of rapid highly-accurate diagnostic tools drives resistance, when presented with an uncertain pathogen or susceptibility profile, providers tend towards over (and possibly unnecessary) prescription. Even where tools exist and are used, for a number of behavioral reasons, a patient with a negative test may still be given an unnecessary drug, further driving resistance. Across diseases, there is a clear need for disease and treatment algorithms to guide provider decision-making and to assist the provider during discussions with the patient. Expanding the use of such algorithms into the informal sector may also help across diseases too.

Sub-optimal adherence favors emergence of resistant pathogens and is a particularly important driver in TB and HIV. Monotherapy was a significant driver for ART resistance until the advent of HAART and for anti-TB drug resistance until the introduction of FDCs. Current malaria guidelines recommend that artemisinin, the only drug to which no resistance has yet been shown, be used in combination, so as to slow the emergence of resistance. Treatment with inappropriate drugs or for the incorrect illness (such as antimalarials for a febrile illness that is not malaria) also drives resistance – this commonly occurs through self-medication for malaria and through inappropriate prescribing of an antibiotic for cholera (in a non-epidemic setting). Across diseases, but particularly for antimicrobials and antimalarials, it is common for a provider to feel (real or perceived) pressure from the patient to treat; and it is often simply easier to prescribe a drug and “close the transaction.” This situation not only compromises patient care, but also drives drug resistance in the longer term.

Table 20 below summarizes key resistance drivers across diseases.

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There is evidence, however, of both willingness of informal providers to engage more firmly with the formal sector and of increased rates of appropriate treatment as a result of this engagement (see Goodman C, W Brieger, A Unwin, S Meek and G Greer. Medicine sellers and malaria treatment in sub-Saharan Africa: what do they do and how can their practice be improved? Am. J. Trop. Med/ Hyg. 77(Suppl 6), 2007, pp.203-218. One example of this is the Tanzanian Accredited Drug Dispensing Outlet (ADDO) Program, which is a network of upgraded informal drug providers who provide primarily non-prescription but also a limited list of approved essential prescription medicines (such as ACTs) through licensed accredited retail facilities (to learn more, see http://www.tfda.or.tz/Addopage1.html
<table>
<thead>
<tr>
<th>Disease</th>
<th>Health system drivers</th>
<th>Behavioral drivers</th>
<th>Drug and drug technology drivers</th>
<th>Other relevant issues identified in the literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Direct and indirect costs of regularly accessing services</td>
<td>Patient factors: Adherence, costs, stigma, side effects, cultural and gender factors</td>
<td>Treatment is complex and lifelong</td>
<td>Recent studies have found that the primary resistance risk (in industrialized countries) is only weakly or is not related to demographic and clinical factors (including ethnicity and viral subtype) (^{230,231})</td>
</tr>
<tr>
<td></td>
<td>Weak regulations governing prescribing/dispensing (increasingly important)</td>
<td>Provider factors: Financial gain, Industry pressure</td>
<td>Second-line ART is not generally available in generic or FDC form (cost and increased pill # can both drive poor adherence)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weak in-patient infection control (blood products, needles)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patient factors: Adherence, costs, stigma, side effects, cultural and gender factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Provider factors: Financial gain, Industry pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB</td>
<td>Direct and indirect costs of regularly accessing services</td>
<td>Patient factors: Adherence, costs, stigma, side effects, cultural and gender factors</td>
<td>Treatment is complex and long; FDCs help with the former</td>
<td>Prior hospitalization is associated with MDR and XDR-TB</td>
</tr>
<tr>
<td></td>
<td>Lack of a high quality, highly accurate diagnostic tool</td>
<td>Provider factors: Financial gain, Industry pressure, Lack of supportive algorithms</td>
<td></td>
<td>Rifamycin resistance is positively associated with HIV infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Together: Real or perceived pressure from the patient to prescribe</td>
<td></td>
<td>In industrialized countries, foreign birth if often a risk factor for resistance(^{232,233})</td>
</tr>
<tr>
<td>Malaria</td>
<td>Lack of, cost of or poor quality services can lead to self-medication</td>
<td>Patient factors: Financial costs, incentive to self-diagnose and medicate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weak regulations governing prescribing/dispensing and lack of or distrust in diagnostic tool can lead to overmedication</td>
<td>Provider factors: Uncertain diagnosis, lack of supportive algorithms</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Together: Real or perceived pressure from the patient to prescribe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shigella</td>
<td>Lack of, cost of or poor quality services can lead to self-medication</td>
<td>Patient factors: Uncertain diagnosis, lack of supportive algorithms</td>
<td></td>
<td>There is significant cross-resistance within drug classes</td>
</tr>
<tr>
<td></td>
<td>Lack of or weak infection control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V. Cholera</td>
<td>Lack of, cost of or poor quality services can lead to self-medication</td>
<td>Patient factors: High and rapid lethality which prompts prescribers and patients to intervene aggressively usually using mass antimicrobial chemotherapy to contain outbreaks(^{234})</td>
<td></td>
<td>Inappropriate use drives resistance</td>
</tr>
<tr>
<td></td>
<td>Weak regulations governing prescribing/dispensing can lead to inappropriate prescribing of antibiotics</td>
<td>Real or perceived pressure from the patient to prescribe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. pneumonia</td>
<td>Lack of, cost of or poor quality services can lead to self-medication</td>
<td>Patient factors:</td>
<td></td>
<td>There is significant cross-resistance within drug classes</td>
</tr>
<tr>
<td></td>
<td>Lack of or weak infection control</td>
<td>Recent antibiotic use is the main factor associated with resistant carriage or transmission, both at the individual and the community levels(^{235})</td>
<td></td>
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</tr>
</tbody>
</table>
What the resistance drivers tell us about cross-disease interventions to slow resistance

To date, most efforts to slow drug resistance emergence and transmission have been disease-specific. Additionally, interventions to slow or remove resistance drivers vary in terms of knowledge about their effectiveness and with regards to their complexity. Review of the literature showed the clear global need for rapid, effective, cheap, accessible, trusted and user-friendly diagnostic and sensitivity testing tools across diseases. Equally important is increased regular monitoring and coordinated drug resistance surveillance. Strengthening supply chain management and regulatory practices are additional possible options to target and would have cross-disease relevance and benefit. The newly-created Medicines Transparency Alliance (MeTA\footnote{See http://www.dfidhealthrc.org/MeTA/index.html}) will certainly help facilitate this (by revealing what is needed to strengthen the system / drug marketplace), but donors and governments alike will need to come behind this as a priority and with dedicated resources. Finally, it is essential to understand what motivates patient, community and provider (both individual and institutional) behavior at the local level and target interventions appropriately.

Issues which merit further research and/or policy dialogue

This review has brought to light several issues which merit further attention, research in some cases, and/or global dialogue in others, to determine their potential role in slowing resistance emergence and transmission. These include:

- Infection with two or more pathogens - how might this drive resistance among drugs to treat the different diseases in question? Specific HIV-TB co-infection questions\footnote{See http://www.dfidhealthrc.org/MeTA/index.html} include:
  - What is the impact of anti-TB drug malabsorption in HIV-infected patients with TB on TB-drug resistance development?
  - What is the impact of co-treatment with anti-TB drugs and ART on resistance development for both types of drugs?
- How does isoniazid preventive therapy drive isoniazid resistance development at the population level?
- To what extent does an immunocompromised status (due to HIV infection, other severe infection or malnutrition) make the individual more susceptible to resistance emergence or infection by a resistant strain?
- What potential might there be for drug cycling? Are there some contexts where circumstances make it more feasible?
- To what extent might vaccines be used successfully as a counter to resistance (and to disease prevalence in general)? The recent failure in developing a successful vaccine against HIV has, to some extent, put a damper on the hope that the success of the pneumococcal vaccine could be replicated for other diseases in the relatively near future. However vaccine development efforts continue, for malaria, for TB, for HIV.
- What potential is there for disease elimination as a method of countering resistance? While clearly not a short-term reality in many cases, malarial disease elimination is currently being considered for Western Cambodia where artemisinin resistance may be emerging\footnote{See http://www.dfidhealthrc.org/MeTA/index.html}.
- How might formal and informal private sector providers be more actively engaged (and thus stick by public sector prescribing/dispensing norms and protocols)? What would motivate them to prescribe more appropriately or not prescribe at all? What lessons are there, for example,
from the experiences of PPM in TB or the Accredited Drug Dispensing Outlet (“ADDO”) Program in Tanzania?

- What is the precise role of pathogen fitness in resistant strains and how does this differ by organism? In this paper we have given little attention to the complicated yet important biological issue of fitness of resistant strains across diseases. This deserves considerable attention both in terms of the implications for drug withdrawal (particularly in the case of malaria) and in terms of the consequences of hospitalizing all extremely-resistant cases together (as with XDR-TB)

- What is an “appropriate/acceptable” level of resistance below which changes to treatment guidelines are not advised? Currently the US Food and Drug Administration (FDA) standard is 10% for antibiotics, but that varies by disease and is influenced by factors like transmission levels. WHO recommends 5% for gonococcus. Some hospital-level protocols include resistance levels as part of the decision-making process but these are hospital-specific, rarely at national level. High-level international policy-making on this matter would necessitate more frequent and reliable (and costly) surveillance reporting systems.

- What role might rapid diagnostics for multiple pathogens play in slowing resistance? To date, there are no rapid diagnostic tests that isolate the etiological agent that is driving the clinical presentation in cases where multiple pathogens may be present (for example, where a child is infected with both S. pneumoniae and sub-clinical P. falciparum, s/he will be treated for malaria based on the positive diagnosis, even if instead, it is pneumonia which is causing the illness). An ideal multi-diagnostic test would be accompanied by clear algorithms to 1) inform treatment (or not) decisions by the provider and 2) help the provider explain his/her treatment (or not) decision to the patient

- Can appropriate incentives be devised to motivate the pharmaceutical industry to incorporate resistance testing at the stage of clinical trials? What are the cost and trial duration implications to “repower” trial sample sizes? Following on this point, what incentives might motivate industry to design drugs that are less likely to develop resistance in the first place? Or that take longer to develop resistance? It is important to recognize the dynamic that resistance creates markets for drug companies - just as 1st line ARVs are going off patent, 2nd line therapies are increasingly needed. Currently drug companies do not have a financial incentive to minimize resistance in some classes. In fact, the financial incentive may be the opposite.

- What potential might “ringfencing” or conserving specific products (perhaps targeting specific population groups such as children, pregnant women and other vulnerable groups) have in slowing resistance? Should entire classes of drugs be “saved” only for prevention or to target resistant strains? Industry’s current incentives impede this sort of policy, but some of the recent proposals to compensate for conservation might be worth exploring further.

**Conclusion**

The literature identified through this review seems to justify the argument for increased global coordination and advocacy around drug resistance instead of each disease community “going on its own.” While there are disease-specific differences in how resistance emerges and is transmitted, these are superseded by the many commonalities across diseases, both in terms of factors driving resistance and effective measures that can be used to slow resistance. Experts in particular disease areas should explore closer collaboration to advocate for getting the issue of drug resistance where it needs to be – in the public spotlight and much higher on the global political and public health agenda.
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• [http://www.who.int/hiv/drugresistance/HIVDRgeneral2006.ppt](http://www.who.int/hiv/drugresistance/HIVDRgeneral2006.ppt)


• Brugha R. Antiretroviral treatment in developing countries: the peril of neglecting private providers. BMJ Volume 326. 21 June 2003


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• Jenny-Avital ER. Acquired rifampin resistance in AIDS-related TB.

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• Talisuna AO, Bloland P, D’Alessandro U: History, dynamics, and public health importance of malaria parasite resistance. *Clin*


V. *Cholerae*


Shigella:


*S. pneumoniae*


• Albrich WC, Monnet DL, Harbarth S. Antibiotic selection pressure and resistance in *Streptococcus pneumoniae* and *Streptococcus pyogenes*. Emerg Infect Dis 2004;10:514-7


Annex I: Search strategy

PUBMED was searched on 6 December, 2007 for all terms except *shigella*, *cholera* and *Streptococcus pneumonia* which were searched for on January 22, 2008. Email alert systems were set up for all search strings below, except first four:

- Resistance + factors contributing to = 903
- Resistance + factors causing = 1011
- Drug resistance + factors contributing to = 373
- Drug resistance + factors causing = 389
- Resistance + HIV + factors contributing to = 37
- Resistance + HIV + factors causing = 22
- Resistance + ART + factors contributing to = 2
- Resistance + ART + factors causing = 2
- Drug resistance + HIV + factors contributing to = 21
- Drug resistance + HIV + factors causing = 16
- Drug resistance + ART + factors contributing to = 1
- Drug resistance + ART + factors causing = 1
- Resistance + TB + factors contributing to = 8
- Resistance + TB + factors causing = 7
- Drug resistance + TB + factors contributing to = 7
- Drug resistance + TB + factors causing = 4
- Resistance + malaria + factors contributing to = 20
- Resistance + malaria + factors causing = 18
- Drug resistance + malaria + factors contributing to = 15
- Drug resistance + malaria + factors causing = 12
- Antimicrobial resistance + factors contributing to = 37
- Antimicrobial resistance + factors causing = 1
- Drug resistance + Shigella + factors causing = 182
- Drug resistance + Shigella + factors contributing to = 45
- Resistance + Shigella + factors causing = 786
- Resistance + Shigella + factors contributing to = 272
- Drug resistance + Cholera + factors causing = 2
- Drug resistance + Cholera + factors contributing to = 0
- Resistance + Cholera + factors causing = 5
- Resistance + Cholera + factors contributing to = 0
- Drug resistance + Streptococcus pneumonia + factors causing = 17
- Drug resistance + Streptococcus pneumonia + factors contributing to = 3
- Resistance + Streptococcus pneumonia + factors causing = 20
- Resistance + Streptococcus pneumonia + factors contributing to = 3

In addition articles by the following authors were searched for (at the suggestion of working group members):

- R. Laxaminaryan
- I. Hastings
- Prudhomme O’Meara
- NJ White


3 http://www.who.int/hiv/drugresistance/HIVDRgeneral2006.ppt


5 Silvia Bertagnolio, WHO/HIV DR team, personal communication

6 ibid.


8 Outterson K. The Vanishing Public Domain: Antimicrobial resistance, pharmaceutical innovation and intellectual property law.


14 Iruka Okeke, personal communication


16 ibid.


18 Nicholas White, personal communication


21 ibid


23 ibid


27 Diane Bennett (WHO), personal communication

34 Ibid.
38 Ibid.
39 Ibid.
40 Ibid.
41 Ibid.
42 Ibid.
43 Ibid.
47 Ibid.
52 Iruka Okeke, personal communication
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82 Tickell S. The Antibiotic Innovation Study: Expert Voices on a Critical Need. React, November 2005


87 Ibid.

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102 Ibid.
103 Ibid.
109 ibid.
110 ibid.
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116 Diane Bennett, personal communication
117 Iruka Okeke, personal communication
118 ibid.


Nicholas White, personal communication


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149 Outterson K. The Vanishing Public Domain: Antibiotic resistance, pharmaceutical innovation and intellectual property law.


151 Suniti Solomon, personal communication


156 Allergy to sulfamethoxazole/trimethoprim and non-adherence: reasons. Tuberculosis (Edinb) 2006; 86:1–10


162 Nancy Blum, personal communication


164 ibid.


61


108 Knut Lonnroth, personal communication


116 Ibid.


119 Nicholas White, personal communication


Iruka Okeke, personal communication

G.T. Keusch, chapter on Shigellosis, in press


PowerPoint presentation received (on January 18, 2008) from and given by Dr. Silvia Bertagnolio. WHO HIVDR team. WHO HIVDR Global Health Network.

Diane Bennett, HIVDR team. WHO HIVDR Global Health Network. Personal communication


Diane Bennett, personal communication


D. Sutherland PowerPoint presentation


Emma Back, personal communication

Iruka Okeke, personal communication


Martha Gyansa-Lutterodt. Personal communication.


Suniti Solomon, personal communication.

Ibid.


Nicholas White, personal communication