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Improving Access to Medicines for Non-Communicable Diseases in the Developing World

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Preface

Non-communicable diseases (NCDs) now account for the lion's share of global morbidity and mortality. Spurred by growing attention to the global devastation caused by NCDs, the United Nations General Assembly will hold a high-level meeting on non-communicable diseases on September 19 and 20, 2011, to "set a new global agenda" on NCDs. In connection with this meeting, this paper provides a first step toward developing a policy research agenda for improving access to NCD medicines in developing countries, a step that the research-based pharmaceutical industry, in particular, can carry forward as part of broader global efforts to combat NCDs. The authors of this paper provide a framework for understanding the various obstacles to access for NCD medicines in the developing world, review specific issues to be confronted within each of these obstacles, identify promising ideas for improving access to NCD medicines, and point to several highly promising areas for the research-based pharmaceutical industry to focus on as it develops its NCD policy research program in close collaboration with other key stakeholders.

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Summary

Non-communicable diseases (NCDs) now account for the lion's share of global morbidity and mortality. Much of the burden is falling on developing countries, whose relatively recent adoption of Western-style health behaviors and lifestyle choices has led to increased prevalence of risk factors for NCDs. At the same time, developing countries also hold the greatest burden of infectious disease, and the rapid increase of NCDs has left countries with under-resourced health care systems to deal with a double burden.

Spurred by growing attention to the global devastation caused by NCDs, the United Nations (UN) General Assembly will hold a high-level meeting on non-communicable diseases on September 19 and 20, 2011, to "set a new global agenda" on NCDs.

Scope and Purpose of This Paper

In connection with the upcoming meeting, this paper is a first step toward developing a policy research agenda, on behalf of the research-based pharmaceutical industry, on how to improve access to NCD medicines in developing countries. This paper is to serve as the basis for further stakeholder consultation, the objective of which is to finalize a policy research program that will be executed by the research-based pharmaceutical industry in close collaboration with other stakeholders.

Given this purpose, the paper focuses narrowly on improving access to medicines, even though health promotion and disease prevention must play a key role in reducing the NCD burden. Because NCDs are not entirely preventable and reversing lifestyle trends and their impact on population health will take time, adequate access to NCD medicines remains essential for mitigating the negative impact of NCDs. This paper also focuses on ideas and innovations that leverage core industry capabilities that, when developed and implemented in partnership with other stakeholders, will improve access to medicines within the constraints that developing countries face today, as opposed to those that would require fundamental systems change and/or economic development.

A Framework for Understanding Obstacles to NCD Medicine Access

Obstacles to access to NCD medicines can arise at and need to be addressed at multiple levels, and understanding the continuum of obstacles is important to developing a coherent policy research agenda. For this purpose, we are proposing a conceptual framework that lays out five

categories of obstacles to NCD medicine access (see Figure S.1). We use this framework to organize evidence for the relative importance of the five categories and to identify promising ideas to overcome them.

Our analysis was based on a literature review combined with Internet-based research on relevant organizations and their activities, as well as on expert and key stakeholder interviews with academic and non-academic researchers and policy experts, officials from national and multilateral organizations, and industry representatives. Based on our review, we propose four priority areas for further research that can produce actionable recommendations for improving access to NCD medicines in the short run.

Toward a Policy Research Agenda for Identifying and Promulgating Best Practices to Improve Access to NCD Medicines

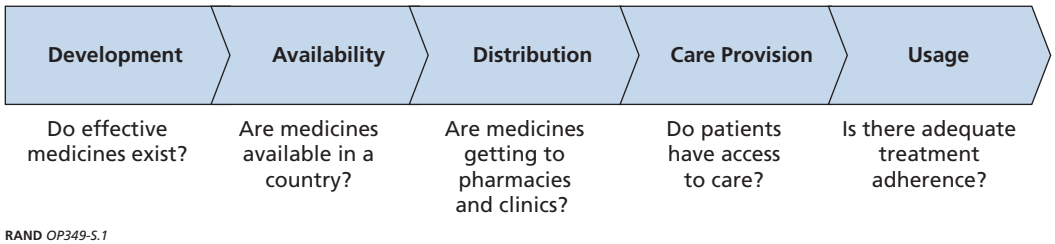
Like many other reviews, ours shows that NCDs present a growing challenge for developing countries and create the real possibility that gains in health that have been made possible by better control of infectious disease and economic development are being eroded. Since NCD medicines offer substantial public health gains, access to medicines is a critical component of NCD care.

Our framework approach identifies structural obstacles across health care systems and ways to systematically overcome them, but it also illustrates that overcoming those obstacles will not be a trivial task. NCDs are the result of multiple causative factors over the course of a life time and require a horizontal, integrated approach to care with the patient, family, and the entire community as active participants. This particular nature of NCDs implies that existing paradigms for improving access to medicines do not provide sufficient answers, because they address obstacles that we find to be less relevant for access to NCD medicines—i.e., drug development and manufacturer prices.

Regarding drug development, many potent NCD medicines have already been developed and will continue to be developed. This is contrasted by the experience with medicines for communicable diseases that predominately affect developing countries, making it more difficult for individual pharmaceutical companies to rationalize and recoup the necessary investment in innovative medicines.

Regarding manufacturer prices, the role they play in impeding access to NCD medicines is minor, since generic alternatives are available for most first-line treatment requirements.

Figure S.1
A Conceptual Framework of Obstacles to NCD Medicine Access



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Schemes to provide medicines to developing countries at differential prices, which are critical to maintaining access to anti-retroviral medicines, are therefore less relevant for many first-line NCD medicines and exist for many NCD medicines that are still under patent protection, such as insulin and inhalers for chronic obstructive pulmonary disease and asthma.

The complexity of the challenge of improving access to NCD medicines means that a multi-stakeholder effort will be necessary to make a fundamental difference. Our goal, however, was more modest in that we were trying to set priorities for the policy research agenda of the research-based pharmaceutical industry. To this end, we focused on promising ideas that build on the industry's core capabilities and that can realistically be implemented. Our analysis points to four areas for further study that emerged from the research we undertook:

1. *Realizing product improvement beyond the chemical compound.* While our analysis revealed that the gains from development of additional compounds will be comparatively small, innovative ways to improve NCD medicine adherence are still dearly needed. We suggest that industry best practices be compiled in the areas of packaging, pricing, and patient education to achieve better drug treatment adherence. A particular focus should be research into the viability of fixed-dose combination products (polypills) for NCD treatment. While conceptually intuitive, the development and manufacturing of polypills are less then straightforward, because a limited range of population-adequate formulations has to be defined and produced at consistent quality. Similarly, regulatory approval may be difficult to obtain, as manufacturers would have to prove safety and efficacy of the co-administration of different compounds.
2. *Enhancing supply chain efficiency and integrity.* We observed that in contrast to what occurs with many consumer products, secure and efficient distribution of NCD medicines is far from guaranteed in developing countries. Availability in poor and remote areas remains limited, hefty markups along the supply chain are common, and the share of counterfeited product is substantial. At the same time, our review points to several creative ideas that should be studied further. A specific area of research could be an assessment of policy options for improving supply chain integrity—for example, a comparison of the potential impact of a public-sector solution to improve supply chain integrity for all medical products with a private-sector approach to marketing medicines, whose value proposition is the security of the supply chain and ability to verify product authenticity.
3. *Achieving gains from regulatory harmonization.* Although potent NCD medicines exist, their availability in developing countries can be hampered by regulatory obstacles. Uncertain timelines and variable requirements for product registration, Good Manufacturing Practice (GMP) inspections, labeling, and product identification codes can increase cost, sometimes to a level that makes product registration prohibitively difficult in a country. Many regional initiatives aim at achieving greater harmonization of regulatory requirements that would allow for increased availability. A logical next step would be to quantify the benefits from regulatory harmonization to promote a data-driven dialog with national authorities, and to promote the optimal use of such available schemes as the World Health Organization (WHO) Certificate of Pharmaceutical Product (CPP) scheme, the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S), and the International Conference on Harmonisation Global Cooperation Group (ICH GCG) scheme.

4. *Improving access to primary care.* We found consistent evidence that limited access to quality primary care is the key obstacle to improving NCD drug treatment. In the absence of a robust primary care system, NCDs go unnoticed until complications arise, adequate treatment is not initiated, treatment effect is not consistently monitored and terminally ill patients do not receive palliative care. At the same time, improving access to primary care is a complex challenge requiring that such fundamental issues as resourcing, governance, and capacity building be addressed. As an initial step, we propose a survey of innovative approaches for delivering effective and efficient primary care in developing countries and an assessment of which of those approaches can be scaled up in which contexts. Our initial review points to several promising ideas to which an in-depth review could add.

We are confident that further research into these priority areas can yield actionable guidance on how to improve access to NCD medicines in the developing world and that the research-based pharmaceutical industry is committed to executing this program. While far from resolving the fundamental issues of preventing and treating NCDs, the evidence generated by this program will allow the industry, in partnership with other stakeholders, to contribute meaningfully to the global efforts to reduce the NCD burden. The UN high-level meeting on NCDs will generate awareness and can galvanize decisionmakers to address the issue. From this can come an opportunity to make sustainable progress, if the attention around the meeting is leveraged to engage all stakeholders in a constructive dialog. Providing evidence-based concrete steps that can be taken in the short run is critical to generating momentum and moving the agenda forward.

Acknowledgments

We are grateful to the Global Health Policy group at the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) for supporting this work and to the NCD Task Force of the IFPMA. We thank Eduardo Pisani and his staff at the IFPMA for coordinating the consultation process with the NCD Task Force members, all of whom provided detailed and constructive feedback and put us in touch with a variety of additional subject matter experts. We also benefited greatly from the insights and observations of numerous academic and non-academic researchers and policy experts, officials from national and multilateral organizations, and pharmaceutical industry experts from member organizations of the IFPMA during our information-gathering process. We thank our colleagues Jack Chow of the Heinz College of Public Policy at Carnegie Mellon University and Homero Martinez and Caroline Fry of RAND, who provided valuable comments and suggestions in their reviews of earlier drafts of this report. Finally, we thank Kristen Haas and Michelle McMullen for providing important administrative support.

Abbreviations

ACE	angiotensin converting enzyme
AIDS	acquired immunodeficiency syndrome
BRIC	Brazil, Russia, India, and China
COPD	chronic obstructive pulmonary disease
CPP	Certificate of Pharmaceutical Product
CTD	common technical document
DALY	disability-adjusted life years
DFID	(UK) Department for International Development
EMA	European Medicines Agency
EMA	European Medicines Agency
EML	Essential Medicines List
EU	European Union
GCG	Global Cooperation Group
GMP	Good Manufacturing Practice
HAI	Health Action International
HIV	human immunodefiency virus
ICH	International Conference on Harmonisation
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
NCD	non-communicable disease
NGO	non-governmental organization
NPHW	non-physician health worker
ODA	Official Development Assistance

OECD	Organisation for Economic Co-operation and Development
PAHO	Pan-American Health Organization
PEN	Package of Essential Noncommunicable
PIASA	Pharmaceutical Industry Association of South Africa
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme
PQP	Prequalification of Medicines Programme
PREMISE	Prevention of Recurrences of Myocardial Infarction and Stroke
RFID	radio-frequency identification
UK	United Kingdom
UN	United Nations
USAID	United States Agency for International Development
USD	U.S. dollars
WHO	World Health Organization

SECTION 1

Introduction

The world's global disease profile is changing: chronic, non-communicable diseases (NCDs)—primarily cardiovascular disease, chronic respiratory disease, diabetes, and cancer—now account for the majority of global morbidity and mortality (World Health Organization, 2011a; Yach et al., 2004, Beaglehole and Yach, 2003). Much of the burden is falling on developing countries,[1] whose relatively recent adoption of Western-style health behaviors and lifestyle choices has led to increased prevalence of risk factors for NCDs. Tobacco use, insufficient intake of fruits and vegetables, and insufficient physical activity are more common in developing countries today as inexpensive, energy-dense foods become more available and populations move from rural areas to urban centers. In addition, the world's population is aging, contributing to the rising prevalence of and mortality rates for NCDs.

Although progress is being made, developing countries also hold the greatest burden of infectious disease, and the rapid increase of NCDs has left underresourced health care systems to deal with a double burden of disease (Boutayeb and Boutayeb, 2005). India, for example, has the highest number of type 2 diabetics in the world (Diamond, 2011) and, in 2008, faced 2.3 million deaths due to cardiovascular diseases (World Health Organization, 2008c). At the same time, more than 2 million people die in India each year from malaria, pneumonia, and diarrhea (World Health Organization, 2008c). Similarly, in Indonesia, communicable diseases account for 41 percent of years of life lost, while NCDs account for 45 percent of years of life lost (World Health Organization, undated-c).

This double burden is particularly straining for under-resourced health systems that historically have focused on care for acute conditions, such as infectious diseases, injuries, and maternity complications. Indeed, current models of care in developing countries tend to be vertically structured, with care delivery being encounter-based for acute conditions or disease-specific care (e.g., HIV/AIDS clinics). However, according to projections by the WHO, ***deaths attributable to communicable disease will approximately halve between 2004 and 2030 in low-income countries, while those attributable to more-chronic NCDs will nearly double*** (World Health Organization, 2008c). If current causal and demographic trends continue, there will be increasing gaps between services provided and services needed, the available and the required health care workforce, and the existing and the required health care plans and budgets.

[1] We primarily use the terms developing countries and developing world when referring to the sample that is the focus of this paper. When appropriate, we use other terms for countries, such as low income, middle income, lower middle income, and least developed. We hold to the World Bank's explanation for its use of developing economies: "The use of the term is convenient; it is not intended to imply that all economies in the group are experiencing similar development or that other economies have reached a preferred or final stage of development." (See World Bank, undated.)

NCDs impede economic, social, and political development in countries that need such development the most because of loss of productivity in the working-age population and cost of care provision (Suhrcke et al., 2006; Adeyi, Smith, and Robles, 2007). In addition, failure to provide care for NCDs can decrease confidence in a national government's ability to provide for its citizens.

A Call to Action

Spurred by growing attention to the global devastation caused by NCDs, the World Health Assembly in 2000 endorsed a global strategy for the prevention and control of NCDs, urging the World Health Organization (WHO) Director-General and member states to prioritize NCD prevention and treatment (World Health Organization, 2008a). In 2008—building off the Framework Convention on Tobacco Control (2003) and the Global Strategy on Diet Physical Activity and Health (2004)—the World Health Assembly endorsed a five-year action plan for implementing the 2000 Global Strategy for the Prevention and Control of Noncommunicable Diseases (United Nations General Assembly, 2010). The action plan focuses on the growing health and economic burden of NCDs in low- and middle-income countries. It identifies six objectives; details specific actions in which member states, the Secretariat, and international partners must engage to ensure achievement of the objectives; and lists performance indicators for measuring progress toward the objectives (World Health Organization, 2008a).

In response to the five-year action plan's fourth objective—"to promote research for the prevention and control of noncommunicable diseases"—the WHO produced a prioritized research agenda (Mendis and Alwan, 2011).[2] Another important result of the action plan was the WHO's development of the Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Settings, which prioritizes cost-effective NCD interventions that integrate NCD control into primary health care (World Health Organization, 2010b). Essential interventions include tobacco cessation for primary prevention of heart attacks and strokes, daily insulin injections for the treatment of type 1 diabetes, and oral or inhaled short-acting β2 agonists for relief of symptoms associated with bronchial asthma. The United Nations General Assembly will hold a high-level meeting on NCDs in September 2011 to "set a new global agenda" on NCDs (World Health Organization, undated-a).

Many other stakeholders are engaged in the campaign to combat the growth of NCDs. For example, four key advocacy organizations formed The NCD Alliance to coordinate advocacy efforts (International Diabetes Federation, 2010). The alliance represents almost 900 member associations and recently partnered with more than 40 NCD researchers and experts to recommend priority interventions for the prevention and control of NCDs (Beaglehole et al., 2011). On the private-sector side, the World Economic Forum attempts to use the workplace to promote healthy lifestyles globally under its Working Toward Wellness initiative (World Economic Forum, 2007). Another contributor to the fight against NCDs is of an entirely different nature but may bear great significance: Michelle Obama, wife of U.S. President Barack

[2] The WHO's prioritized research agenda identifies important areas of research that are, in general, broader than those identified in this paper. A few of the narrower priorities identified in the WHO's research agenda align with those that we have identified; such instances are noted throughout this paper.

Obama, has adopted as her signature issue the battle against childhood obesity (Associated Press, 2010).

Access to NCD Medicines in the Context of Prevention

Because unhealthy lifestyles are one of the driving forces behind NCDs in the developing world, the first line of defense ought to be disease prevention and health promotion. This priority has long been recognized by the WHO, the United States Agency for International Development (USAID), the United Kingdom (UK) Department for International Development (DFID), and other national governments and development organizations. But NCDs are not entirely preventable, and reversing lifestyle trends and their impact on population health will take time. Thus, adequate medical treatment of manifest NCDs and access to NCD medicines—the focus of this paper—are essential for mitigating the negative impacts of NCDs. Unfortunately, however, ***it is often the case that fewer than half of diagnosed patients receive indicated medicines***, in spite of proven effectiveness (Joshi et al., 2008). For example, the WHO-PREMISE (Prevention of Recurrences of Myocardial Infarction and Stroke) study found that treating coronary heart disease patients with aspirin, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, or lipid-lowering medicines lowers the risk of future vascular events by about one-quarter each; appropriate combinations of these medicines, however, can prevent recurrences by between two-thirds and three-quarters (Mendis et al., 2005). The authors also estimate that the four-medicine regime combined with smoking cessation and lowered blood pressure can lower the risk of recurrence by more than four-fifths. Thus, although we focus here on access to NCD medicines, we do recognize the importance of health promotion and disease prevention as critical areas that must be addressed in parallel.

Objectives of This Paper

The high-level meeting of the United Nations (UN) General Assembly on the prevention and control of NCDs scheduled for September 2011 will bring unprecedented attention to the global NCD challenge and will create high expectations that governments and civil society will take effective actions. Much of the work going into the meeting has focused on developing a better understanding of the NCD burden in the developing world and on NCD prevention efforts. Data availability certainly needs to be improved, and prevention of NCDs through healthy lifestyles and risk factor control will be a critical component in containing this emerging challenge. Our focus here, however, is somewhat different. ***No matter how effective prevention efforts are, manifest NCD will remain a significant challenge for years to come, and ensuring access to medicines should remain a top priority.*** Achieving this goal will require improved understanding of the gaps in medicine access, prioritization of those gaps, and identification of promising innovations to close those gaps.

Thus, with the high-level UN meeting coming up, this paper represents a first step toward developing a policy research agenda, on behalf of the research-based pharmaceutical industry, on how to improve access to NCD medicines in developing countries. The purpose of the paper is to serve as a basis for further stakeholder consultation to help the industry finalize a

policy research program that will be executed in close collaboration with other stakeholders as the next step.

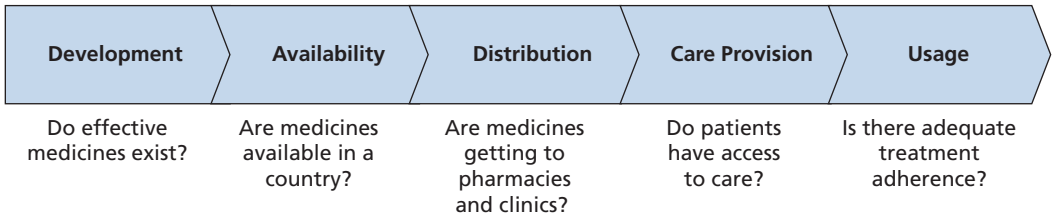
Given this purpose, the paper focuses narrowly on improving access to medicines, even though health promotion and disease prevention must play a key role in reducing the NCD burden. As NCDs are not entirely preventable, and reversing lifestyle trends and their impact on population health will take time, adequate access to NCD medicines will remain essential for mitigating the negative impact of NCDs. The paper also focuses on ideas and innovations that leverage core industry capabilities, which when developed and implemented in partnership with other stakeholders, will improve access to medicines within the constraints that developing countries face today, as opposed to those that would require fundamental systems change and/or economic development.

A Framework for Considering Barriers to NCD Medicines

Issues around product availability and product pricing tend to dominate the discourse on drug treatment access in developing countries. Although these are valid concerns, particularly for newly developed compounds, ***a much broader range of issues needs to be understood and addressed to ensure that those afflicted with NCDs in developing countries have access to medicines*** and, ultimately, to health care services that detect, monitor, and control diseases, resulting in positive health and economic outcomes. This range of issues includes everything along the continuum from appropriate research and development efforts to ensure effective medicines exist for the populations of interest to medicines reaching patients' hands and patients adhering to their medicine regimens. In Figure 1.1, we present a simple conceptual framework that follows this continuum and lays out the major issues or potential obstacles along the way—that is, those related to the development of effective medicines, the availability of those medicines in the country or jurisdiction of interest (i.e., related to product importation and registration policies and procedures), the distribution of those medicines throughout the country (i.e., related to the robustness and completeness of the supply chain), the provision of those medicines for patients in need (i.e., related to access to health care services and an appropriately trained health care workforce), and the usage of (or adherence to) those medicines by patients (i.e., related to patient beliefs and costs).

In this paper, we utilize this framework as a means for ensuring that the full range of obstacles is recognized, the obstacles' underlying causes are laid out, and innovative ideas for addressing each obstacle are identified for further study.

Figure 1.1
A Conceptual Framework of Obstacles to NCD Medicine Access



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Scope and Research Approach

We focus our discussion on the four major NCD conditions that are the largest contributors to the global burden of disease: cardiovascular disease (particularly coronary artery disease and congestive heart failure), chronic respiratory disease (particularly chronic obstructive pulmonary disease [COPD]) and asthma), diabetes, and cancer (United Nations General Assembly, 2011).[3] In some sections of this paper, we address cancer separately because cancer care (other than palliative care) requires treatment in specialty care settings, which is not the case for other NCD conditions, whose treatment can mostly be provided in primary care settings. We consider access to medicines for these conditions in developing countries, giving special consideration to Brazil, Russia, India, and China (BRIC) since they collectively represent a significant portion of the global NCD disease burden.

Our research was based on a literature review focusing on the global burden of disease and the development, availability, distribution, provision, and use of medicines for NCDs in the developing world. We also completed Internet-based research on relevant organizations and their activities in this area. Simultaneously, we conducted about 50 expert and key stakeholder interviews with academic and non-academic researchers and policy experts, officials from national and multilateral organizations (including the Directorate General of Health Services in India, the WHO, the World Bank, and the Pan-American Health Organization [PAHO]), advocates for specific NCD awareness and care (such as the International Union Against Tuberculosis and Lung Disease, the International Insulin Foundation, the International Diabetes Federation, and the Union for International Cancer Control), and pharmaceutical industry experts from member organizations of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), all of whom work on issues related to NCDs in various regions and countries around the world.

Organization of This Paper

Section 2 provides an overview of the evidence on the increasing burden of NCDs in the developing world, as well as the evidence for treatment gaps. In Section 3, we discuss each of five categories of obstacles proposed in our conceptual framework; in Section 4, we review innovative and promising initiatives, programs, and practices that have been implemented in countries or regions of interest. Section 5 summarizes our findings, and we conclude with a proposed policy research program in Section 6.

[3] We prioritized this core group of NCDs because they represent the largest contributors to morbidity and mortality, but we realize that conditions beyond this core group, in particular mental health conditions, add to the burden of disease in developing countries.

SECTION 2

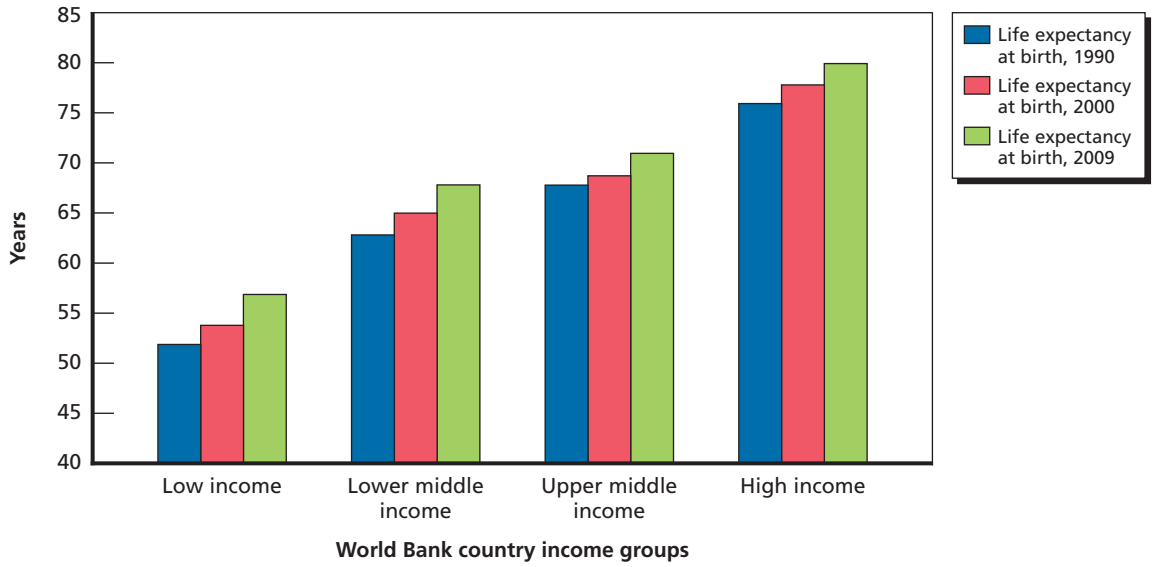
The Increasing Burden of NCDs in the Developing World

NCDs account for 36 million deaths annually—more than 60 percent of all deaths worldwide—and cardiovascular disease, cancer, chronic respiratory disease, and diabetes are the most common causes of mortality (World Health Organization, 2011a). NCDs also account for nearly half of all disability-adjusted life years (DALYs) worldwide (Stuckler, King, and McKee, 2008), and have a particularly negative impact on developing countries, where 80 percent of NCD-related deaths take place (World Health Organization, 2011a). Furthermore, the proportion of the total burden of NCDs in developing countries has grown by about 10 percent since 1990 (Miranda et al., 2008).

Several modifiable risk factors contribute to NCD prevalence, most notably tobacco, physical inactivity, excessive alcohol consumption, and unhealthy diet (World Health Organization, 2011a). In the last two decades, these risk factors have become increasing prevalent in developing countries, because of population shifts from rural to urban areas, increased availability of inexpensive, energy-dense food, and industrialization. The prevalence of physical inactivity, for example, rose dramatically in the first decade of the century, from a 43 percent increase in Indonesia (2003 to 2008) to a 188 percent increase in China (2002 to 2008) and a 334 percent increase in Russia (2003 to 2008) (World Health Organization, 2011c, undated-b). Over the last decade, obesity rates increased by 24 percent in Russia, 84 percent in Brazil, 97 percent in China, and 171 percent in India (World Health Organization, 2011c, undated-b). Tobacco use rose dramatically in some places (for example, from 29.4 percent in 1999 to 57 percent in 2008 for Indian men) but appeared to level off in Russia, China and other countries as public health campaigns began to take effect (World Health Organization, 2011c, undated-b).

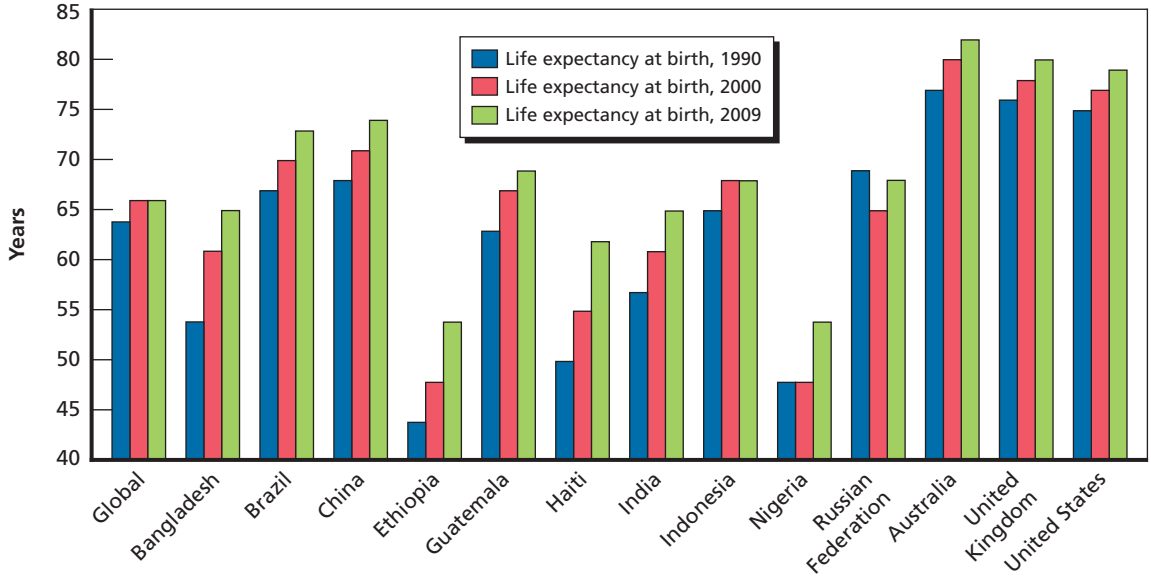
Increased life expectancy contributes to the rise of NCD prevalence (World Health Organization, 2008c). Overall, life expectancy has been increasing in countries at every income level (see Figure 2.1), but the most dramatic gains have been observed in low-income and lower-middle-income countries (see Figure 2.2) (World Health Organization, undated-c). For instance, life expectancy in Bangladesh jumped from 54 years in 1990 to 65 years in 2009 and life expectancy in Ethiopia and Haiti rose from 44 to 54 years and from 50 to 62 years, respectively. Much of this increase is attributable to progress made in combating the spread of infectious disease. In other words, progress in medicine and public health, combined with economic development, has allowed the populations in poorer countries to achieve lifespans during which they experience chronic disease.

Figure 2.1
Life Expectancy by Income Group, 1990 to 2009



SOURCE: World Health Organization, undated-b.
RAND *OP349-2.1*

Figure 2.2
Life expectancy in Selected Countries, 1990 to 2009



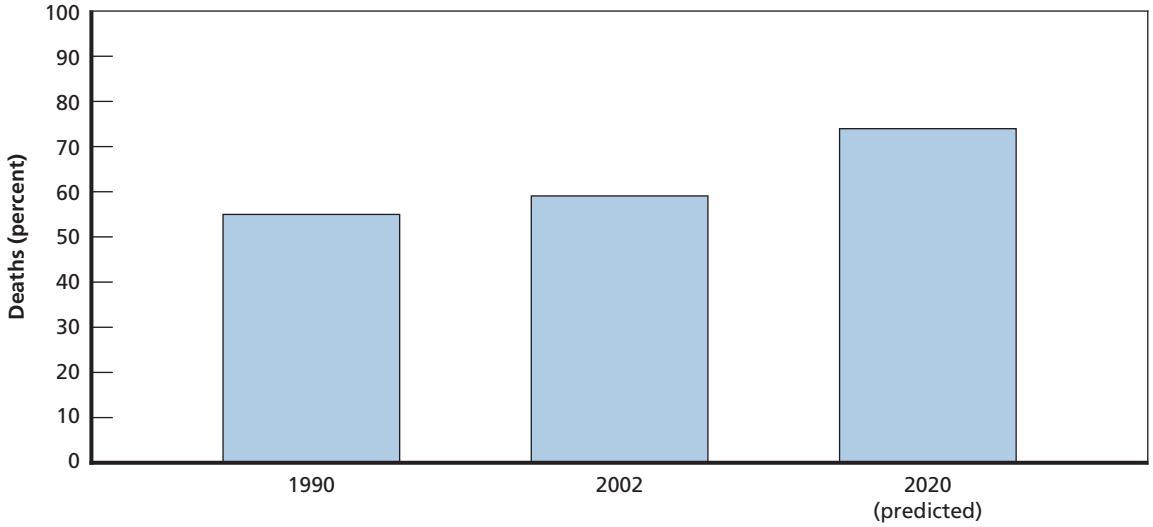
SOURCE: World Health Organization, undated-b.
RAND *OP349-2.2*

The Shift from Communicable to Non-Communicable Disease

In 2008, 65 percent of deaths worldwide were caused by NCDs, more than twice as many as were caused by communicable diseases (26 percent) (World Health Organization, 2011d), and the shift to NCDs is continuing as shown in Figure 2.3. For instance, between 2000 and 2004, HIV/AIDS (human immunodeficiency virus/acquired immunodeficiency syndrome) prevalence declined by 17 percent globally, 19 percent in Africa, and 33 percent in Southeast Asia, but diabetes prevalence increased by 26 percent globally and 35 percent in Africa. Asthma prevalence increased by 15 percent in Africa, and COPD prevalence nearly doubled in Southeast Asia. Further, the lion's share of the projected increase in NCD burden occurs in low- and middle-income countries, where it is expected that infectious diseases will decline while cardiovascular disease, cancers, and other NCDs rise (see Figure 2.4).

Despite the increasing burden of NCDs in the developing world, donor funding is lacking, particularly in comparison to funding available for infectious diseases. A 2008 study published in the Lancet estimated that, in 2005, funding for NCDs from the world's four largest health donors—the World Bank, the U.S. government, the Bill and Melinda Gates Foundation, and the Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria—was about $3 USD (U.S. dollars) per death, compared to $1,030 USD per death for HIV/AIDS (Sridhar and Batniji, 2008). In addition, the study demonstrated a large discrepancy between the diseases responsible for the greatest burden in low- and middle-income countries and those that were the focus of disease-specific funding. As shown in Figure 2.5, ***HIV/AIDS received significantly more funding per death than any other disease with a similar burden, while NCDs received the least despite their significantly greater burden.***

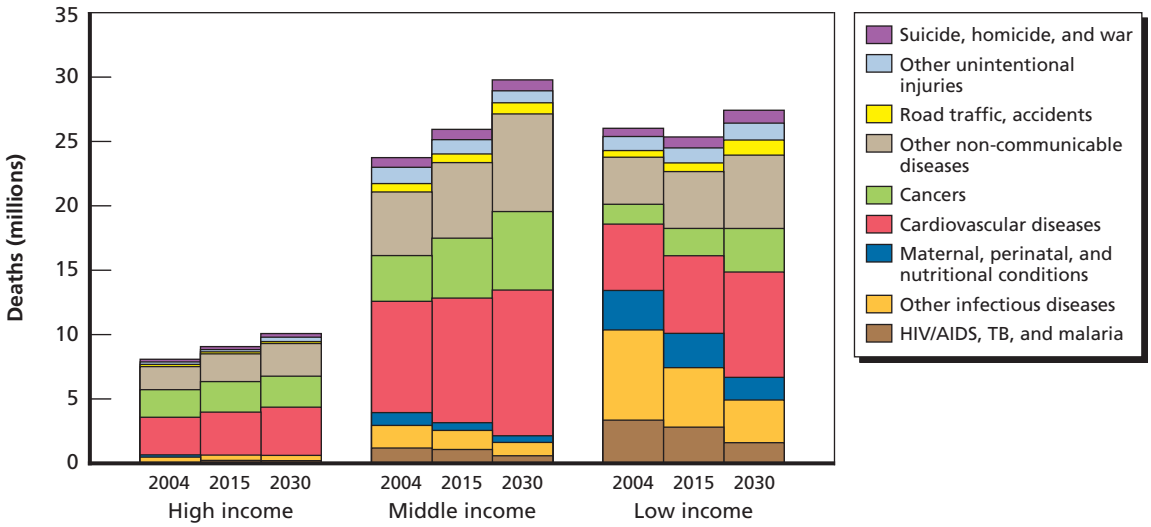
Figure 2.3
Global Mortality from Chronic Diseases



SOURCE: Data from Yach et al., 2004.

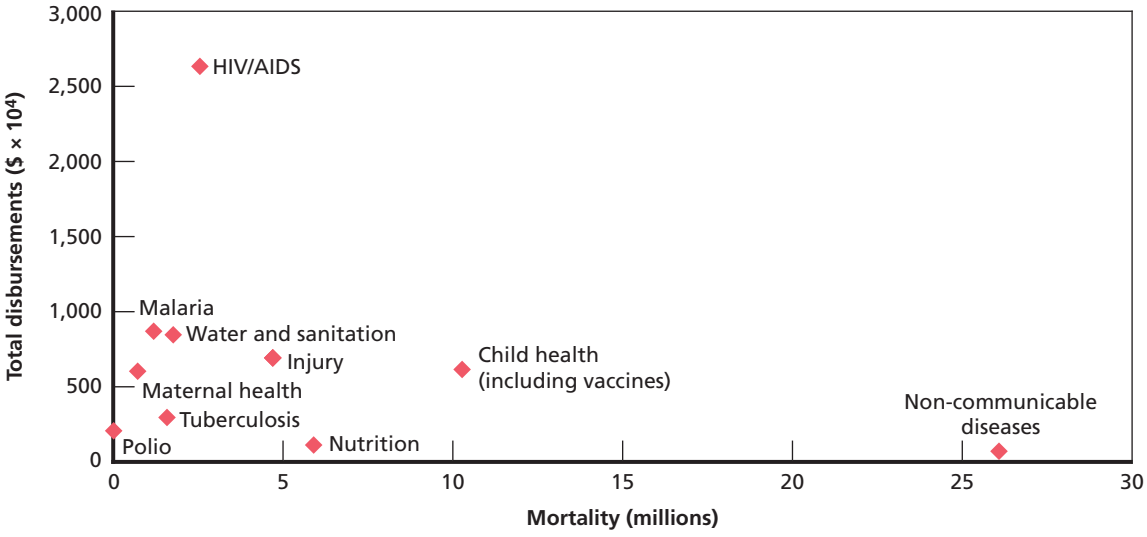
RAND *OP349-2.3*

Figure 2.4
Projected Deaths for High-, Middle-, and Low-Income Countries, by Cause



SOURCE: World Health Organization, 2008c.
RAND *OP349-2.4*

Figure 2.5
2001 Worldwide Mortality Versus 2005 Disbursements



SOURCE: Sridhar and Batniji, 2008.
NOTES: (1) 2001 worldwide mortality vs. 2005 disbursements of World Bank, U.S. government, Bill and Melinda Gates Foundation, and Global Fund to fight AIDS, Tuberculosis and Malaria. (2) Health-systems funding cannot be represented as a graph because there is no reliable way to measure mortality and disability due to the absence of a good health system. The omission of health-systems funding excludes about one-third of all World Bank disbursements from this figure.
RAND *OP349-2.5*

Thus, although Official Development Assistance (ODA) for health has increased over the past decade, this trend has been due, predominantly, to funding for HIV/AIDS in sub-

Saharan Africa. ***ODA to the health sector in 2007 reached $22.1 billion USD, of which less than 1 percent was dedicated specifically to NCDs.*** The true figure is likely slightly higher, as about 5 percent of ODA went to basic health services which may fund NCD control (Kates, Lief, and Pearson, 2009).

The Four Major NCD Conditions

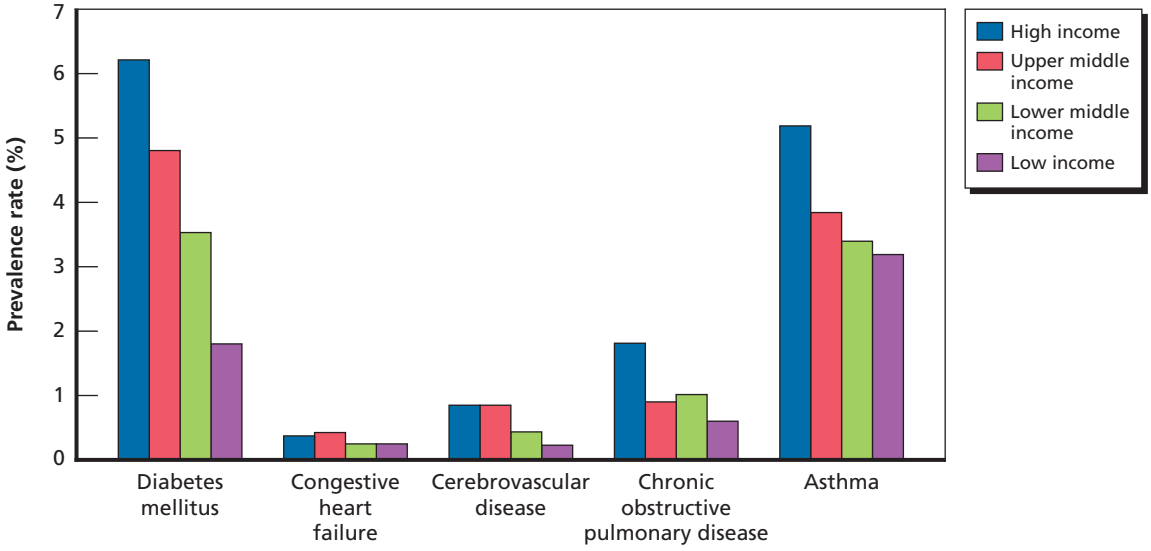
Data from 2004 demonstrate that prevalence rates for the major NCDs in low-income and lower-middle-income countries are approaching those in upper-middle-income and, in some cases, high-income countries (see Figure 2.6). In particular, the prevalence of COPD and congestive heart failure in lower-income countries is similar to that in upper-middle-income and high-income countries.

GLOBOCAN estimated that between 2008 and 2030, cancer incidence will increase 1766 percent in Africa and will increase in the Americas 87 percent among low- and middle-income countries and 56 percent among high-income countries. Dans et al. (2011) demonstrated that for Southeast Asian countries, ***NCDs account for the highest proportion of deaths in high-income countries, but NCD death rates are highest in low-income countries.*** That is, people are more likely to die from NCDs in lower-income countries than in higher-income countries. In addition, people in lower-income countries die at younger ages, affecting productivity and economic development.

The Economic and Social Impacts of NCDs

The high prevalence of NCDs in developing countries poses significant economic and social threats. Costs associated with NCDs affect individual patients and their families, as well as

Figure 2.6
Prevalence of Selected Causes, by Income Level



SOURCE: World Health Organization, 2008d.

RAND *OP349-2.6*

health systems and national productivity. The WHO estimates that between 2005 and 2015, heart disease, diabetes, and stroke will be responsible for losses to the national incomes of India, Russia, and China of $237 billion USD, $303 billion USD, and $558 billion USD, respectively (World Health Organization, 2005). The cost of diabetes care alone constitutes between 2.5 percent and 15 percent of national health care budgets; in India—the country with the highest number of diabetics—up to a quarter of a family's income may be devoted to treatment of a diabetic family member (Atkins, 2005). Furthermore, the prevalence of NCDs in the working-age population is greater in developing countries than in developed countries, which adversely affects productivity in the developing world (Yach et al., 2004). Dans et al. (2011) report that about 30 percent of all deaths from NCDs in Southeast Asia occur in people age 15 to 59, representing premature mortality in a large proportion of the region's labor force. By 2030, more than 50 percent of the projected nine million deaths due to cardiovascular disease in China will be in the working-age population (Leeder et al., 2004).

The fact ***that greater proportions of the working-age populations in developing countries suffer from NCDs has not only a significant economic impact, but also a significant social impact***. Leeder and colleagues (2004, p. 36) explain that since more working-age men than working-age women have heart disease, "workforce CVD [cardiovascular disease] deaths in men also cause havoc for married women by making them widows. Notwithstanding the death toll among women, the higher heart disease rates among young men in the prime of life mean that CVD is creating an equivalent cohort of widows who need support for decades." The household disruption caused by adult death and disability also affects children; in many developing countries that lack systems of care for the disabled, adults who suffer a disability are cared for by children, especially girls (Leeder et al., 2004). Often, these children must abandon school to serve as caretakers (Leeder et al., 2004). Finally, aging populations in much of the developing world lead to higher prevalence of NCDs and, as a result, greater economic and social burdens on families, communities, and countries.

A Comment on Data Availability

The available data clearly point to a rising prevalence of NCDs globally and the increasing contribution of NCDs, in comparison to infectious diseases, to mortality rates. However, projection models are responsible for much of the available data on the burden of NCDs in the developing world. Many developing countries do not produce cause-specific death certificates and do not conduct regular surveillance of risk factors that could more accurately predict future NCD rates. Thus, although projections provide us with broad trends and the implications of those trends for health and health policy, we have limited access to specific data by disease and by country.

Furthermore, the robustness of the projections very much depends on the validity of the assumptions they are built on—primarily the assumption that the trends and relationships between variables found in higher-income countries will be replicated in lower-income countries (Mathers and Loncar, 2006). Whether these assumptions hold, will be known only when better data become available through the implementation of surveillance and disease registry systems and consistent and detailed death certificates. Such data, including now absent data on co-morbidities, will be critical for a better understanding of the true burden of disease at a

national level and thus for designing effective health policies and interventions to address the gaps.

Gaps in NCD Drug Treatment

The evidence for gaps in NCD drug treatment in developing countries is still quite limited. However, available evidence suggests there are substantial gaps in the prevention, diagnosis, and treatment of NCDs. ***Limited access to safe and effective medicines represents only a piece of a much larger picture, as effective treatment is hampered by overall limited health system resources and capacity*** (e.g., lack of public health campaigns to promote public awareness; lack of continuing education for health care providers) and limited health literacy of patients. That is, treatment gaps stem from a lack of the following: patient *awareness* of NCDs and their symptoms, *care-seeking* for the potential condition, *diagnosis* of the condition by a health care provider, *instruction* on medical or non-medical treatment regimens, and *adherence* to medical or non-medical treatment regimens.

For example, a recent study of hypertension prevalence, awareness, treatment, and control in Mozambique found that only 18 percent of hypertensive patients were aware of their condition (Damasceno et al., 2009). Among those that were aware, only half received treatment. Reports of diabetes awareness rates in Peru indicate that awareness of disease can be as low as 14 percent—and of that 14 percent, only about 40 percent receive treatment (García et al., 2007). Even in the BRIC countries, awareness of NCDs is low: In conducting a survey of Russian health perceptions, behaviors, and conditions, the Association of International Pharmaceutical Manufacturers found that while 13.1 percent of Russians have cardiovascular diseases, only 7.5 percent identify as having such diseases (AstraZeneca, 2011). NCD awareness rates in developed countries are regularly higher; for example more than 80 percent of Americans with hypertension are aware of their condition and more than 70 percent receive treatment (Egan, Zhao, and Axon, 2010). These findings point to the importance of public awareness and access to primary care (in addition to access to affordable, appropriate medicines) in ensuring NCD treatment.

In the WHO-PREMISE study, which investigated secondary prevention of cardiovascular disease in ten low- and middle-income countries, researchers found that patient use of medicines was insufficient despite the availability of cost-effective medicines (Mendis et al., 2005). Among patients with coronary artery disease, nearly 20 percent did not receive aspirin, 52 percent did not receive a beta-blocker, 60 percent did not receive an ACE inhibitor, and 79 percent did not receive a statin. The authors of the study identified several potential causes of the medicine gaps, such as health providers failing to implement clinical practice guidelines, affordability of some medicines, selective prescription of medicines to only certain categories of patients, lack of diagnostic equipment and facilities, and lack of health care workforce capacity. Thus, despite the availability of cost-effective interventions, they were not being implemented due to lack of health system capacity for managing chronic care, lack of national drug policies, and lack of continuing education for health care providers.

Hospedales et al. (in press) report that in Latin America and the Caribbean, half of the diabetics and one-third of the cases of hypertension go undiagnosed, almost one-third of those with diagnosed diabetes and half of those with diagnosed hypertension do not take appropriate medication, and more than half of those with diagnosed diabetes and one-quarter of those

with diagnosed hypertension are uncontrolled. In contrast, only 16 percent of diabetics in the United States do not receive indicated medicines (Centers for Disease Control and Prevention, 2011). While lack of access to medicines certainly plays a role in the lack of medication usage, the undiagnosed and uncontrolled cases in Latin America and the Caribbean point to systemic weaknesses. Thus, while the evidence remains limited, the gaps in NCD treatment are clearly substantial.

SECTION 3

Barriers to Access to NCD Medicines

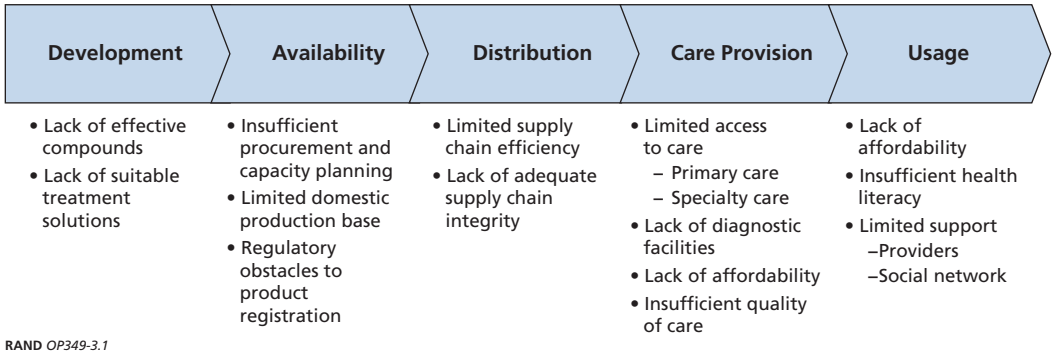
As stated earlier, prevention of NCDs through healthy lifestyles and risk factor control will be a critical component in containing this emerging challenge in developing countries. Adequate treatment of manifest disease will, however, remain necessary. Use of medicines will be a cornerstone of treatment since medicines that effectively control symptoms and decelerate disease progression exist. Our analysis suggests that ***NCD medicine use is much lower than clinically necessary***, and one of our purposes is to help understand the underlying causes of this gap in care.

As a first step, we propose a framework for describing and categorizing obstacles to NCD drug treatment access. As described in Section 1, this framework has five components that capture different obstacles along the continuum from research and development to create a medicine to the medicine reaching a patient. Here, we explore each of these obstacle categories in greater detail by analyzing the underlying reasons for such barriers and prioritizing their importance in contributing to the NCD treatment gap in the developing world. Figure 3.1 provides an overview of the underlying reasons, each of which is discussed throughout the remainder of this section.

Development: Do Effective Medicines Exist?

The epidemiologic transition from infectious to non-infectious diseases as the main cause of mortality occurred in developed economies several decades ago. Consequently, development

Figure 3.1
Underlying Reasons for Obstacles to NCD Medicine Access



of NCD medicines has long been viable from a business perspective—so long, in fact, that ***many potent NCD medicines are now available as generics***. This contrasts with the situation for some communicable diseases (such as trypanosomal parasitic infections) that solely or disproportionately affect developing countries, and for which safe and effective medicines are still lacking. Further, additional medicines will continue to be developed.

We analyzed the state of NCD medicine development by assessing two criteria. First, we reviewed whether effective chemical compounds have been developed to treat cardiovascular disease, chronic respiratory conditions, diabetes and cancer. Second, we evaluated whether these developed medicines constitute suitable treatment solutions for developing countries by looking into their effectiveness in diverse populations, the availability of adequate medicine delivery systems, and the stability of the medicines under likely conditions in those countries.

Existence of Effective Medicines

To determine the state of medicine development for NCDs, we conducted a clinical review to find out which types of medicines are required to treat the four major NCDs. We compared our list to the WHO Essential Medicines List (EML)[1]—to identify whether the current EML contains at least one medicine in each category (World Health Organization, 2011b).[2] We also determined whether at least one potent medicine in each category has probably lost its patent protection, i.e., is likely to be available in generic form.[3] Following the WHO classification, we indicated whether a medicine is labeled as "core" on the EML (i.e., considered minimum medicine need for a basic health care system) or as "complementary" (i.e., essential medicine for a priority disease for which specialized diagnostic or monitoring facilities, specialist medical care, and specialist training are needed). We reviewed medicines for non-cancer NCDs, cancer treatment, and palliative care separately.

Non-Cancer NCDs. Table 3.1 lists the key medicine categories for the treatment of asthma, COPD, coronary artery disease, congestive heart failure and diabetes, along with active compounds in these categories that are included on the WHO EML. Not surprisingly, our review showed that potent medicines used as first-line treatment have been developed in all categories. In addition, we found that at least one potent compound in each category was likely to have lost its patent protection and was therefore likely to be available in generic form.

Insulin represents a special case. Complex medicines like insulin, which are often referred to as biologics, are substantially more difficult to manufacture than the so-called small molecule medicines. It is typically not possible for a follow-on producer to manufacture fully identical biologics. Follow-on biologics are thus referred to as biosimilars, which have a varying degree of interchangeability with the original product. Consequently, it is substantially more demanding to obtain regulatory approval for biosimilars than for small molecule medicines,

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[1] The WHO EML is a biennially updated core list of minimum medicine needs for a basic health care system. It is commonly used by Health Ministries to prioritize drugs for inclusion in national formularies.

[2] To avoid redundancy, we listed drug categories being used for several diseases only once. For example, ACE inhibitors are listed under congestive heart failure but are also used in diabetes care.

[3] For this paper, we were not able to systematically ascertain patent status of a medicine in every country, but we are confident that our assessment is correct for most countries in our sample. Similarly, the actual availability of a generic version of a given drug depends on the jurisdiction. For example, a generic alternative may not yet be registered or the currently marketed version of compounds may still be protected by other patents, those covering, for instance, extended release formulations or combination products.

Table 3.1
Review of Non-Cancer NCD Medicines on WHO EML

Condition	Drug Category	Active Ingredient	Patent Protection Expired?
Asthma/COPD	Short-activing beta-agonists	Epinephrine	Yes
	Long-acting beta-agonists	Salbutamol	Yes
	Inhaled corticosteroids	Beclometasone	Yes[a]
		Budesonide	Yes[a]
	Vagolytics	Ipratropium	Yes
	Systemic corticosteroids	Prednisolone	Yes
		Dexamethasone	Yes
Coronary artery disease	Anti-platelet drugs	Acetylsalicylic acid	Yes
	Nitrates	Glyceryl trinitrate	Yes
		Isosorbide dinitrate	Yes
	Beta-blockers	Bisoprolol	Yes
	Lipid-lowering drugs	Simvastatin	Yes
	Calcium channel blockers	Verapamil	Yes
		Amlodipine	Yes
	Other antihypertensives	Methyldopa	Yes
Congestive heart failure	Diuretics	Hydrochlorothiazide	Yes
		Furosemide	Yes
		Amiloride	Yes
		Sipironolactone	Yes
	ACE inhibitors	Enalapril	Yes
	Anticoagulants	Warfarin	Yes
	Inotropic agents	Digoxin	Yes
	Other vasodilators	Hydralazine	Yes
Diabetes	Oral hypoglycemic	Glibendamide	Yes
		Metformin	Yes
	Short-acting insulin	Various	Yes[b]
	Depot insulin	Various	Yes[b]
	Insulin antagonists	Glucagon	Yes

SOURCE: RAND review of WHO EML (World Health Organization, 2011b).

[a] While inhaled steroids as active ingredients are no longer protected by patent, some delivery technologies for the inhalers are still protected.

[b] Several insulin products have lost their patent protection, but others are still protected. The availability of biosimilar insulin products in a given jurisdiction depends on its regulatory framework for biosimilars.

since sufficient interchangeability needs to be demonstrated and can differ more widely by jurisdiction. Thus, even though significant patent protections have expired for selected short-acting and long-acting insulins, the availability of biosimilar insulin depends on the jurisdiction. In the United States and the European Union (EU), laws and regulations are now in place to permit the approval of insulin biosimilars, but none are yet marketed. In India, China, and many developing countries in Latin America, however, follow-on insulins have been marketed for many years.

In spite of the availability of potent generic options, there are still development needs for non-cancer NCD medicines. Innovative medicines can have fewer side effects, can be more convenient to use (e.g., once daily), and can have greater potency for refractory cases. But, at minimum, ***first line medicines that treat non-cancer NCDs are currently not constrained by the lack of available compounds, and the patent protection of all key compounds has expired.***

Cancer Care. Given its different biology, cancer requires fundamentally different treatment from that needed for other NCDs. Whereas the treatment goal for other NCDs is to

prevent progression and control symptoms, the ultimate target of cancer care, at least in the early stages, is cure. Cancer treatment is also different in that early detection is imperative and primary therapy for most cancers consists of surgery and/or radiation. Chemotherapy is used as primary treatment mostly for lymphomas and leukemia, as adjuvant treatment to enhance cure rates of surgery and/or radiation, and as palliative treatment in advanced stages. For hormone-sensitive cancers, like some types of breast and prostate cancer, hormone deprivation therapy is used to inhibit tumor growth. With the exception of screening and palliative support measures (such as pain therapy), cancer care is delivered mostly by specialists at secondary and tertiary care facilities, as opposed to in primary care settings. This implies that access to specialty care, such as medical and surgical oncologists, radiation treatment and specialty labs, is a precondition for pharmacotherapy of cancer.

Because cancer's underlying biologic mechanisms are not well understood, drug treatment for cancer has historically consisted of non-specific and highly toxic compounds that aim to destroy cancer cells faster than normal cells. This strategy has proved successful in achieving high cure rates for selected malignancies, such as childhood leukemia, testicular cancer and selected lymphomas. But for the vast majority of cancers, traditional chemotherapy yields only incremental (and sometimes small) gains in life expectancy, at the expense of substantial side effects. The compounds required for most standard chemotherapy protocols are listed on the current WHO EML. The EML also contains the hormonal antagonist tamoxifen for breast cancer treatment, but not anti-androgen medicines for prostate cancer treatment. In recognition of oncologists' key role in cancer pharmacotherapy, all medicines are reserved for the supplemental list.

Only recently, the growing understanding of cancer biology has allowed the research-based pharmaceutical industry to develop agents that can exploit cancers' genetic and molecular dependencies to, at least in theory, target malignant cells while limiting side effects. Some of these medicines have proven spectacularly effective as they indeed control previously deadly malignancies; others, however, lead only to small increases in life expectancy. In addition, their targeted nature implies that they are only effective in the subset of patients whose cancer has a specific genetic or molecular dependency. While this specificity means that medicines can be highly effective and have fewer side effects, their development costs need to be spread over smaller populations, leading to a higher cost per case. The emergence of those targeted therapies, and the existence of a robust, molecularly based research pipeline, has caused numerous debates about implications for the financial sustainability of health care systems even in high-income countries. Given their higher cost per case and the substantial infrastructure requirements for matching patients to medicines, even beyond the requirements for conventional cancer treatment (e.g., specialty labs, trained oncologists), none of the newer targeted medicines is currently listed on the EML.

Palliative Care. At terminal stages of communicable and non-communicable diseases alike, drug treatment focuses on controlling symptoms rather than curing. Medicines are used for pain therapy, sedation, and depression treatment to alleviate suffering and to ameliorate gastrointestinal symptoms that can arise from the disease or its treatment. The WHO EML contains several medicines in each category on the core list, and the patent protection has expired on all of them (as Table 3.2 shows).

Table 3.2
Review of Palliative Care Medicines on WHO EML

Drug Type	Active Ingredient	Patent Protection Expired?
Non-opioid analgesics	Acetylsalicylic acid	Yes
	Ibuprofen	Yes
	Paracetamol	Yes
Opioids	Codeine	Yes
	Morphine	Yes
Antidepressants	Amitriptyline	Yes
	Fluoxetine	Yes
Sedatives	Diazepam	Yes
	Midazolam	Yes
Constipation treatment	Docusate sodium	Yes
	Lactulose	Yes
	Senna	Yes
Antiemetics	Cydizine	Yes
	Dexamethasone	Yes
	Hyoscine hydrobomide	Yes
	Ondansetron	Yes

SOURCE: World Health Organization, 2011b.

Suitability as Treatment Solutions

Effectiveness and Safety in Specific Populations. The development of increasingly targeted medicines has led to the emergence of the field of personalized medicine, since some of these medicines will be effective or safe only in a population that shares certain genetic traits. The best-known examples are targeted cancer medicines that only work in a subset of patients with a defined mutation. The selective nature of such medicines means that their effectiveness and safety cannot necessarily be extrapolated beyond the population in which they were originally tested. Because many clinical trials, particularly for novel medicines, are conducted in developed countries (and thus mostly on patients of European descent), targeted medicines may not be similarly safe and effective in developing countries whose populations have different genetic traits. In addition, the infrastructure for detecting the subset of patients likely to respond to such targeted medicines may not exist in developing countries, as mentioned above.

Testing in diverse populations will thus be critical in the continued development of highly targeted medicines, in particular for cancer treatment. Limited data exist on the comparative safety and effectiveness for the current first-line NCD medicines, but industry experts believe this to be a minor issue because the non-selective nature of those medicines makes them less dependent on specific genetic traits. In addition, non-cancer NCD medicines are usually titrated to effect (for instance, for blood pressure or cholesterol control) and can thus be adjusted based on patients' responses. And even older cancer medicines target ubiquitously available cell structures rather than specific mutations and are therefore likely to be effective across populations. One residual area of concern is genetic differences in medicine metabolism, which can lead to differences in side effects. Genetic diversity will become a greater issue for innovative, more-targeted medicines, in particular for cancer treatment.

Development of Appropriate Medicine Delivery Technology. Development gaps can also exist in the technologies used to deliver medicines safely and effectively. This issue arises particularly for medicines that are not taken orally.

Delivering medicines via inhalers is an attractive treatment option for patients with asthma or COPD because the medicines can reach the bronchial tissue directly, which allows for faster

onset of action and less systemic absorption, reducing side effects. Inhaled corticosteroids are a mainstay of asthma treatment, whereas systemic steroids are mostly used for acute exacerbations or refractory cases because of the substantial side effects of long-term treatment. Highly effective and user-friendly inhaler technologies have been developed, from simple inhalers to spacers and disk inhalers that facilitate delivery of the active compounds to the lower respiratory tract.

Because insulin has to be injected, patients need to learn proper injection techniques. They also must learn how to fill the accurate insulin dose from a vial into a syringe. To avoid this additional step, companies have developed insulin pens, which are pre-filled syringes that allow the user to select a dose by turning a dial. Such pens are widely available for patent-protected insulins but not yet for biosimilars.

Stability of Medicines Under Extreme Climates. The NCD medicines on the WHO EML contain reasonably stable compounds that do not have special requirements for storage and transportation, such as a cold chain. Some medicines, such as insulin, are believed to deteriorate when exposed to extreme temperatures, which could limit their usability in some countries. However, Sanofi-Aventis, which produces the insulin medicine Lantus, found that Lantus gained impurities but did not lose activity when stored at 95 to 102 degrees F (35 to 39 degrees C) for one month (Grajower et al., 2003). These data suggest that extreme temperatures may not impose as substantial an obstacle to insulin stability as is widely believed.

Summary

Our analysis shows that a large array of medicines for NCD treatment has been developed. At least one potent alternative in each therapeutic category for the first-line treatment of non-cancer NCDs and palliative care is likely to be available in generic form, implying that those medicines should be affordable in all but the poorest settings. Given the degree of under-treatment of NCDs, as we show below, ***the most immediate gains in health can be achieved by improving access to existing medicines, as opposed to developing new compounds.***

Development needs still exist for second- and third-line medicines for refractory cases, to reduce side effects in the treatment of non-cancer NCDs, and for palliative care. And for many cancers, effective first-line medicines still have to be developed. As mentioned above, a fundamental discussion will be required in the long run on how to maintain incentives for development of highly targeted medicines, especially in cancer care, while ensuring access to care for patients in developing countries. However, ***as the anticipated impact of highly targeted medicines is currently small from a population health perspective, we believe that this discussion is less important than the other priorities*** we have identified for further policy research.

Availability: Are the Medicines Available in the Respective Countries?

In this subsection, we look at the obstacles to the availability of NCDs at the country level. Our central question is, Are NCD medicines available in a country and, if not, why? We focus on country-level characteristics, such as regulations and bureaucratic processes, insufficient

data for adequate procurement planning, and the lack of domestic manufacturing—all of which limit the availability of needed NCD medicines in a country.[4]

Procurement and Capacity Planning

The chronic nature of NCDs should theoretically make forecasting the demand for associated medicines easier than forecasting the demand for medicines—such as antibiotics—that treat acute conditions. But we find substantial evidence for a mismatch between supply and demand in many developing countries. Several policy experts, local providers, and representatives of non-governmental organizations (NGOs) identified two key reasons for the difficulty of forecasting demand: a lack of accurate data on disease prevalence and medicine needs, and poor coordination and communication between local health workers and the often-centralized planning bureaucracies. This is true for planning of both national and regional demand and is especially prominent in rural and remote areas.

For example, Mali, Mozambique, and Zambia base their insulin demand forecasts on past consumption, which can result in significant discrepancies between supply and demand. In Mozambique, 77.3 percent of insulin was allocated to the Maputo Province, where the capital city lies but which represents just 11.3 percent of the total population. Such unbalanced availability also contributes to significant differences in estimated life expectancies: An individual 15 or more years of age suffering from diabetes is expected to have a 20-year life expectancy in Maputo compared with just above 5 years on the national level (Beran, Yudkin, and de Courten, 2005).

Especially in countries that depend on development assistance, ***lack of coordination between donor agencies, as well as the commonly "vertical" (disease-specific) nature of donor programs, further impedes accurate capacity planning***. In such countries, multiple stakeholders—international organizations, public and private donor organizations, national governments, and others—are involved in planning decisions. These stakeholders often work within competing frameworks and incentive structures and may not be aligned with local procurement.

Domestic Production Base

Some of the economically more-developed countries, such as the BRIC countries and Indonesia, have a strong local production base, especially for generic medicines. In some countries, the government has actively promoted the local production of generics, leading to a dominant position of domestic producers. But many low- and middle-income countries, in particular those located in sub-Saharan Africa, have no or only a rudimentary local pharmaceutical industry and are dependent on imports. Some experts support strengthened local manufacturing capacity in these countries in order to lower medicine prices and increase economic development (United Nations Conference on Trade and Development, 2011; Médecins Sans Frontières, undated). However, a World Bank technical report warned that "if a developing country with manufacturing facilities is able to finish off bulk active ingredients sourced from developed or

[4] It should be noted that in the literature, availability is often used next to affordability to distinguish the two key elements of medicine "accessibility." Such a definition (not to be confounded with our use of the term) is used, for example, by the Project on Medicine Prices and Availability—a collaboration between the WHO and Health Action International (HAI) that aims to improve price transparency and measures availability as "the percentage of medicine outlets in which the medicine was found on the day of data collection." (Health Action International, undated.)

other countries *at high costs*, such manufacture may have *no impact whatever on patient access to* needed medicines" [emphasis added] (Kaplan and Laing, 2005, p. iii). Or differently framed: "from a public health point of view it does not matter where the medicine comes from as long as it is safe, affordable and of good quality" (Anderson, 2010).

While fear of supply insecurity, increased demand driven by donor funding or exemption from some international patent rules, and the hope for lower prices have been listed as arguments for local manufacturing in developing countries, both quality and affordability are not easily ensured by local manufacturing. Especially for Africa, "local manufacturing remains a difficult issue since compliance with international standards within Africa varies significantly" (Rägo, Sabartova, and Sawyer, 2010, p. 958). In addition, unreliable water and electricity supplies, required imports of active pharmaceutical ingredients, machinery, and packaging, as well as the lack of skilled human resources, tend to drive the production cost up (Anderson, 2010), making the rationale behind local manufacturing sometimes doubtable. As a senior WHO official said, "Local production is not a panacea. The tragedy is that it is sometimes promoted blindly" (Anderson, 2010, p. 1598). Thus, further research into the impact of strengthened local manufacturing bases in developing countries may be useful, and—at this point—efforts to strengthen such bases should not be a top priority.

Market Regulation

Pharmaceutical products have to be registered with the local drug authority to ensure quality, safety, and efficacy.[5] However, onerous processes and the lack of robust, sustainable regulatory frameworks that allow for predictable and efficient outcomes can impede market access, especially in markets with insufficient regulatory capacity. Our analysis points to significant variation in requirements for product registration, renewal, and Good Manufacturing Practices (GMPs),[6] as well as in the related timeframes in developing countries.

Product Registration. Product registration procedures in developing countries are typically country specific and require knowledge of local regulations. ***Requirements for product registration can vary, with clear guidelines missing and insufficient regulatory capacity to guarantee quality, safety, and efficacy*** (as is the case with 90 percent of African regulatory authorities responsible for medicine registration) (African Medicines Regulatory Harmonisation Consortium, 2010).

The WHO found that none of the 26 assessed sub-Saharan countries had adequate and sustained funding for operation of their national medical regulatory authority; that these authorities were lacking qualified staff, especially with respect to marketing authorization and inspections; that the capacity to assess the application for an innovator medicine was almost

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5 "In general terms, the data that might not be required [for generics compared to original products] would be clinical trials; the remainder of the information needed would be the same as for an NCE [new chemical entity]. Generic products […] can be registered on the basis of chemical comparisons alone (e.g. dissolution data), bioequivalence data or clinical trials" (Hill and Johnson, 2004, p. 24).

6 GMPs "provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the cGMP [current Good Manufacturing Practice] regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations. This includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories." (U.S. Food and Drug Administration, 2009.)

non-existent; and that only three out of the 26 organizations had detailed technical guidelines in place (World Health Organization, 2010a).

Existing mechanisms, described in more detail in Section 4, that support such resource-constrained regulatory authorities include the following. Unfortunately, these mechanisms are not always applied to their full advantage.

1. The WHO Certificate of Pharmaceutical Product (CPP) scheme (World Health Organization, undated-b), in which proof of registration by a recognized competent authority can facilitate registration in another country.
2. The option of obtaining an assessment under the European Medicines Agency's (EMA's) Article 58 provision.
3. The WHO's Prequalification of Medicines Programme (PQP), which ensures that medicines meet acceptable standards of quality, safety, and efficacy. The PQP is increasingly used by international donors and developing countries to guide their choices when it comes to purchasing medicines (World Health Organization, 2010c),

Requirements for clinical trials or bioequivalence data also vary significantly in their detail (Bate et al., 2010). Hill and Johnson (2004, p. 24) assert that "generic product registration does vary from country to country, and within a country there are variations in the data required depending on the type of generic."

These country-specific standards are viewed by many industry experts as a crucial obstacle to registering their products in developing countries. For example, 90 percent of the respondents in a survey conducted by the Pharmaceutical Industry Association of South Africa (PIASA) perceived the lack of harmonized standards as an obstacle to registration in African countries (Narsai, 2010)

In a recent assessment of registration procedures in 12 low- and middle-income countries, Bate et al. (2010) found significant variation in the average length of the registration process. They also discovered that timelines can vary for locally produced and imported medicines, as well as for generic and patented products (see Table 3.3).

Table 3.3
Registration Duration in Selected Countries

Duration of registration							
Brazil	Russia	China	India	Kenya	Nigeria	Uganda	Vietnam
Original: 12–14 months Similar: 8–12 months Generic: 6–8 months Fast-track: 2.5 months	Local: 6–12 months Import: 18 months Fast-track: 3 months	Original: 2–3 years Import: 18 months	Original: 12–18 months Import: 12 months	Regular: 12 months Fast-track: 3 months	Regular: 3 months	Regular: 3–6 months New: 12 months Fast-track: 1–3 months	Regular: 6 months

SOURCE: Bate et al., 2010

Within this set of countries, China tended to have the longest registration timelines, with two to three years for original medicines, up to 18 months for imported generics, and even longer for vaccines. In Russia, the registration of imported medicines also took, on average, 18 months, while in India and Brazil, registration of an original product took only 15 months and 13 months, respectively (Bate et al., 2010). It should also be factored in that ***in many emerging markets, product registration can only commence following an approval by a recognized competent authority, which can delay submission by at least 12 months***.

Similarly, the WHO assessment of 26 sub-Saharan African countries found that time frames for the assessment of applications ranged from three months to five years, notwithstanding the fact that the "overall assessment time frames were long, little time was available for a thorough in-depth assessment by experts due to scheduling difficulties and backlog" (World Health Organization, 2010a).

In the PIASA survey, respondents stated that only about half of the medicines were registered in less than two years, while in more than a third of the cases the process took more than three years. This lengthy process, as well as its variability, was mentioned as a major obstacle to marketing a medicine in Africa (Narsai, 2010). But lengthy processes are not limited to the African registration process, as was emphasized by an Indonesian health care provider, who stated that registration in Indonesia can take up to two years. Several industry experts mentioned experience with unpredictable registration processes (including complicated notarization procedures, additional sample provision, and undue review processes applied to products that have already been approved by a stringent regulator). This ***unpredictability of the registration process in developing countries can deter companies from registering their products***.

Especially if the market is small, country-specific packaging requirements are a potential obstacle to market access, given that many pharmaceutical companies have rationalized their manufacturing sites and standardized processes in order to create centers of excellence around the world that supply the medication. In Africa, however, more and more countries are introducing country-specific requirements (e.g., specific labeling requirements, including that companies print scheduling status and registration numbers on the medicine packaging). These ***country-specific requirements have, in some cases, led companies to stop supplying their medicines to the countries***.

Several industry representatives and policy experts expressed concerns about the integrity of bureaucratic procedures in developing countries. Administrative processes can be unintentionally or even intentionally opaque and influenced by nepotism and corruption (Bate et al., 2010).[7] A survey by Bate et al. (2006) found "non-official" charges and "unnecessary delays" to be common (see Table 3.4). In particular, in light of such regulations as the U.S. Foreign Corrupt Practices Act, which makes it unlawful and imposes high civil and criminal penalties for U.S. companies who make payments to foreign government officials to assist in obtaining business, companies may decide to avoid entering markets because of compliance risks. Similarly, many pharmaceutical companies have strict policies to not pay bribes, potentially leading to obstacles to product registration (International Federation of Pharmaceutical Manufacturers and Associations, 2006).

[7] Obviously opaque processes and corruption can affect access to medicines at many levels. We discuss these issues at this point because product registration is the first point of contact with local authorities.

Table 3.4
Survey Results on Tariffs, Bribes, and Unnecessary Delays

Country	Number of Cases/Tariffs Paid	Unnecessary Time Delay (>24 Hours Beyond Subjectively Expected Good Practice)	Exporter/ Importer Incurred Some Legal Cost	Non-Official Administrative Charge	Non-Official Other Charge	Bribe Demanded
Uganda	14/12	14	4	6	11	3
Ethiopia	11/9	11	2	4	11	3
Nigeria	21/18	17	4	13	18	7
Kenya	18/16	16	3	9	14	6
Vietnam	12/8	4	5	3	12	10
China	14/12	12	0	1	12	3
India	15/14	15	3	4	15	4
Total	105/89	89	21	40	93	36

SOURCE: Bate et al., 2006

GMP requirements can also pose an obstacle to market entry and thus availability, if they are not harmonized in small markets, as is the case in Ghana, Nigeria, Togo, Kenya, Uganda, Tanzania, and Mozambique (Narsai, 2010). In a PIASA study, between 46 and 70 percent of responding companies mentioned that GMP inspection fees were too high and could deter registration in a country (Narsai, 2010).

Furthermore, the WHO assessment of 26 countries in sub-Saharan Africa found that only five national authorities had published GMP guidelines that met WHO standards (three of the five were directly taken from the WHO text) (World Health Organization, 2010a). The assessment also found shortages of qualified inspectors and a need for inspector training in GMP (World Health Organization, 2010a). While opportunities to make the GMP inspection process more efficient through such mechanisms as the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S)[8] exist, they do not seem to have been adequately implemented by developing countries.

Post-Marketing Surveillance. Some of our policy experts and industry representatives stated that the pharmacovigilance systems in many developing countries are insufficiently resourced, a conclusion also reached by some reviews (World Health Organization, 2010a). This suboptimal use of limited resources can aggravate significant shortcomings with respect to pharmacovigilance once products have entered the market. However, this is an important area in which local capacities and a well-established network for monitoring potential problems are crucial. In addition, the local cultural beliefs about adverse events, especially those related to the concomitant use of traditional medicines, need to be understood.

[8] The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) are two international instruments between countries and pharmaceutical inspection authorities that aim to foster co-operation in the field of GMP.

Distribution: Are the Medicines Getting to the Point of Dispensing to the Patient?

In this subsection, we look at the distribution of medicines within a country to the outlets, such as pharmacies and health centers, that dispense them to the patient. We cover supply chain efficiency (such as reaching rural areas) and supply chain integrity (such as counterfeiting and diversion). Although the term *supply chain* often has a broader definition,[9] we focus here on the efficiency and integrity of distribution within a country. Our reason for doing this is that our review suggests that ***obstacles to NCD medicine access arise from distribution issues within countries themselves, as opposed to distribution through the global supply chains that deliver products to the national point of entry***. In many developing countries, the distribution of medicines in the public sector is operated separately from distribution in the private sector.

Supply Chain Efficiency

While in even the most remote areas of the world, consumer goods—such as beverages, shampoo, and mobile phone cards—are readily available, medicines are often not, despite the fact that most commonly used medicines do not require particular shipping conditions and could be distributed through the same channels as consumer goods.

Segmentation of Supply Chain(s) for Medicines. Especially in low-income countries that depend on donor assistance, supply chains are commonly segmented horizontally and vertically. Horizontal segmentation means that international donors coordinate the delivery of medicines to the point of entry and then leave the distribution to local organizations. As there is often little coordination, under-resourced local organizations face the daunting task of preparing for the distribution of unpredictable supplies. Vertical segmentation means that separate supply chains are maintained for different diseases or donor agencies. Kaufmann, Miller, and Cheyne (2011, p. 1117) found that in Kenya, "twelve different types of health commodities, [were] provided by at least eighteen different donor organizations, procured by thirteen different agencies, sent to five different warehouses, delivered through seven different supply chains to a single recipient: the health service provider." Clearly, such highly fragmented processes are not just inefficient, but also make it difficult to generate reliable data for supply planning.

Urban Versus Rural Availability—Domestic Distribution and the Challenge of the "Last Mile." Distribution to rural or remote areas seems to be a critical obstacle to NCD medicine access in developing countries. While major cities typically have a reasonably robust infrastructure, local "spokes" (e.g., health centers, health posts, or community health care workers) often cannot be supplied reliably because of impassable roads, unreliable electricity, and isolated locations (Hayford, Dumm, and Levine, 2011). The lack of physical infrastructure is made worse by a lack of qualified staff (Ooi, 2008). To illustrate, a study in Zambia found that insulin was available in all 13 hospitals but in only 42 percent of community health centers (Beran, Yudkin, and de Courten, 2005).

Weak Supply Chain Management. Our industry and policy experts identified several significant challenges:

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[9] See, for example, Mentzer et al., 2001, citing Christopher (1992), who understands it as "the network of organizations that are involved, through upstream and downstream linkages, in the different processes and activities that produce value in the form of products and services delivered to the ultimate consumer."

- lack of standardized information systems
- inefficient inventory accounting and management practices
- lack of trained supply chain managers
- limited tracking and tracing mechanisms
- poor storage facilities and conditions
- stock theft.

The result is increased transportation and inventory costs, a dearth of reliable data to forecast future demand, significant imbalances between local demand and supply, increased waste, and vulnerability to breaches of supply chain integrity.

Supply Chain Integrity

Supply chain integrity means that a product arrives undiminished in quality and quantity via the intended route to the intended end-user, and that the supply chain is not infiltrated by counterfeit medicines. Typical threats in the context of medicines are the circulation of unregistered and counterfeited products, diversion, and the use of expired products. ***Breaches of the supply chain integrity can not only result in a loss of products and the unintended and harmful use of substandard products, but can also undermine trust in the quality of the health care provision.***

Circulation of Unregistered and Counterfeited Products. In many developing countries, substantial proportions of circulating medicines are unregistered. When taking office in 2001, for example, the former head of the Nigerian drug agency, Ms. Dora Akunyili, found that about 68 percent of all circulating medicines were unregistered and 41 percent were counterfeited (Integrated Regional Information Networks, 2007). Bate et al. (2010) cite several studies that estimated that after a huge campaign against counterfeited and unregistered medicines, the National Agency for Food and Drug Administration and Control managed to reduce the share of unregistered medicines to 14 percent by 2006. In Brazil, studies estimated that 30 percent of the medicines on the market were unregistered, and 330,000 cases of unlicensed medicines were registered in China in 2007 alone, most of which were linked to "fly by night" firms. In Russia, where about 1,000 tons of unregistered medicines were seized between 2002 and 2005, some manufacturers reportedly resorted to the production of unregistered medicines to increase profits (Bate et al., 2010).

Such bypassing of formal registration processes is often accompanied by a lack of GMP licenses and a lack of quality control. In many countries, unregistered medicines are found not just on the black market, but also in regular hospitals and pharmacies. According to a local academic and medical doctor, doctors themselves sometimes procure medicines on the black market if they are not available through official channels.

The WHO reported that 60 percent of the confidentially received reports between January 1999 and October 2000 came from developing countries and could be grouped in the following categories of irregular medicines:

- products without active ingredients: 32.1 percent
- products with incorrect quantities of active ingredients: 20.2 percent
- products with wrong ingredients: 21.4 percent
- products with correct quantities of active ingredients but with fake packaging: 15.6 percent

- copies of an original product: 1 percent
- products with high levels of impurities and contaminants: 8.5 percent.

While more-recent data at that level of detail are not available, ***worldwide estimates put the share of counterfeit medicines at 10 percent of the medicines market, and it is estimated that 25 percent of medicines—an even more alarming figure—are counterfeited in developing countries (World Health Organization, 2010e)***. Moreover, a detailed sampling in Africa and Southeast Asia even found that 30 to 60 percent of medicines were substandard (Harris, Stevens, and Morris, 2009). In 2006, at least 100 people in Panama died after ingesting counterfeited syrup from China that contained diethylene glycol (McGinnis, 2008, Bix et al., 2007). In 2008, contaminated cough syrup caused the deaths of 84 children in Nigeria (Harris, Stevens, and Morris, 2009). Such cases not only harm individuals, they also undermine the trust of patients and providers in the safety and effectiveness of medicines and in their governments' ability to protect patients' interests.

Diversion. Medicines originally donated or sold under special conditions such as "in support of a public health program" can be diverted for other purposes and can be found in the domestic private market—either "formal" or "informal." Even re-imports to countries ineligible for the acquisition under these special conditions are common, according to one of our industry experts. Sometimes, medicines sold to least-developed countries under differential pricing schemes are actually imported back into the country of production. A recent case of diversion was reported in Nigeria, where antiretrovirals procured under a public health program were sold on the streets of Nairobi without prescription (Siringi, 2004).

Care Provision: Are Medicines Being Provided to Patients in Need?

Even in developed countries, managing patients with chronic conditions remains a challenge because health care systems have evolved around the direct patient-provider encounter, which is appropriate for acute conditions but does not provide the ongoing support and management that chronically ill patients require (Goroff and Reich, 2010; Samb et al., 2010). As a result, ***many chronically ill patients remain under-treated, even in well-resourced health care systems***. A recent study analyzing the World Health Survey that the WHO conducted in 70 countries found that only 50.6 percent of respondents with a chronic condition in high-income countries reported having access to treatment; the percentages in low-income and lower-middle-income countries were even lower: 32 percent and 37.5 percent, respectively (Wagner et al., 2011). Or, as one interviewee put it, "Continuity of care is not working in systems as advanced as the U.S. and Switzerland, so how can we expect that this would work in resource poor countries?"

In spite of the availability of low-cost, potent NCD medicines, treatment gaps are substantial in developing countries. For example, "in China, India, and low- and middle-income countries of Europe and Latin America, awareness of having hypertension ranges between 35 and 46 percent, and among those diagnosed with hypertension, only 20 to 40 percent receive treatment" (Adeyi, Smith, and Robles, 2007, p. 976). Obstacles to NCD medicine access at the care-provision level can arise in several areas, which we discuss below. The degree to which those obstacles impede access to NCD medicines can vary substantially by geographic location and socioeconomic status within a given country (Miranda et al., 2008).

Access to Primary Care

Our analysis suggests that ***limited access to primary care for NCDs is a key impediment to access to treatment*** in many developing countries, as most NCD conditions are managed in primary care settings. Availability of primary care providers—and, as a result, access to primary care—tends to increase with country income level: According to World Bank data, low-income countries have, on average, 0.18 physicians and 0.53 nurses for every 1,000 people, compared with one physician and 1.69 nurses per 1,000 in lower-middle-income countries, and almost three physicians and eight nurses per 1,000 for Organisation for Economic Co-operation and Development (OECD) countries. This shortage is caused by both limited entry (due to under-investment in education and job training) and high attrition rates (due to poor working environments, low pay, and better career opportunities in wealthier countries) (Chen et al., 2004). Shortages tend to be worse in rural areas (Reddy et al., 2005; Samb et al., 2010).

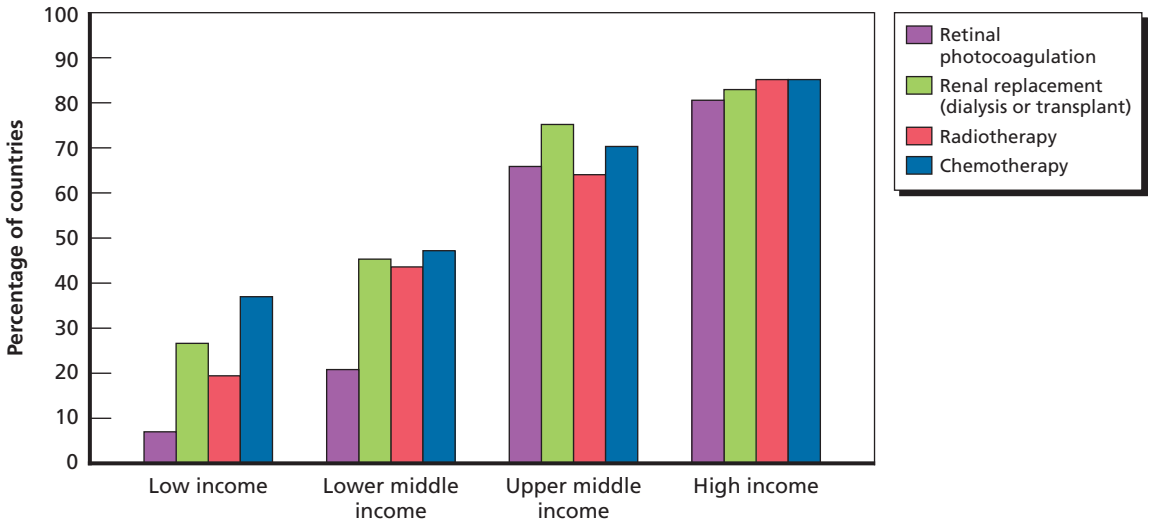
In developing countries, primary care services are provided by both the public and private sectors. The public sector is usually organized around a network of care centers, with primary and community health centers in more-remote and rural areas and district, tertiary, and teaching hospitals in urban areas. The private sector comprises a wide range of provider types, including sole practitioners, not-for-profit and non-governmental institutions, and for-profit facilities (Berendes et al., 2011). Public-sector care is commonly subsidized, while the private sector offers greater convenience. There is considerable variation in the quality of care between public and private institutions and also between different types of private providers. In addition, within the health workforce in a number of developing countries, it is not uncommon for staff—especially doctors—to work in the public sector, engaging in private fee-for-service care in order to supplement their incomes (Bangdiwala et al., 2010). One of the consequences of limited access to primary care is delayed diagnosis of NCDs and insufficient management of diagnosed disease, which leads to detection at advanced stages or when patients experience acute exacerbations, both commonly resulting in hospital admissions (World Health Organization, 2011a).

Access to Specialty Care

Specialty care in developing countries is mostly provided in secondary and tertiary care hospitals, and is even more capacity constrained than primary care. ***The limited availability of and concentration in hospitals of specialty care is a particular obstacle for rural areas.*** For example, in Ethiopia, the majority of diabetics living in rural areas have to travel over 40 km to reach the nearest hospital, while 23 percent have to travel more than 100 km, and 13 percent more than 180 km (Alemu and Watkins, 2004). Similarly, some patients in Zambia, Mali, and Mozambique have to travel more than 1,000 km to the nearest hospital (Beran, McCabe, and Yudkin, 2008).

Many developing countries lack specialists and facilities for NCD treatment, particularly because of their historic focus on acute care. In Vietnam, for example, specialty training in endocrinology and diabetology is relatively recent; as a result, only a few doctors are considered specialists in these fields (Beran and Higuchi, 2011). As data from the WHO's 2010 NCD country capacity survey show, care for diabetic complications, such as retinopathy and renal failure, is often not available (see Figure 3.2). ***Access to cancer care beyond surgery is also limited: Less than 20 percent of public health systems in low-income countries provide radiation treatment, and less than 40 percent provide chemotherapy. Specialized cancer centers are often only available in one or two hospitals in the capital city of low-income and lower-middle-***

Figure 3.2
Availability of Selected Procedures for Treating NCDs in Public Health Systems



SOURCE: World Health Organization, 2011a.
RAND *OP349-3.2*

income countries, which creates substantial obstacles to treatment beyond availability of drugs (CanTreat International, 2010).

Vertical funding structures that favor communicable diseases such as HIV/AIDS have exacerbated the problem, as little funding is made available for NCD care. Cancer in particular has been neglected in many low- and middle-income countries, with only about 5 percent of global expenditures on cancer going to these countries (Farmer et al., 2010).

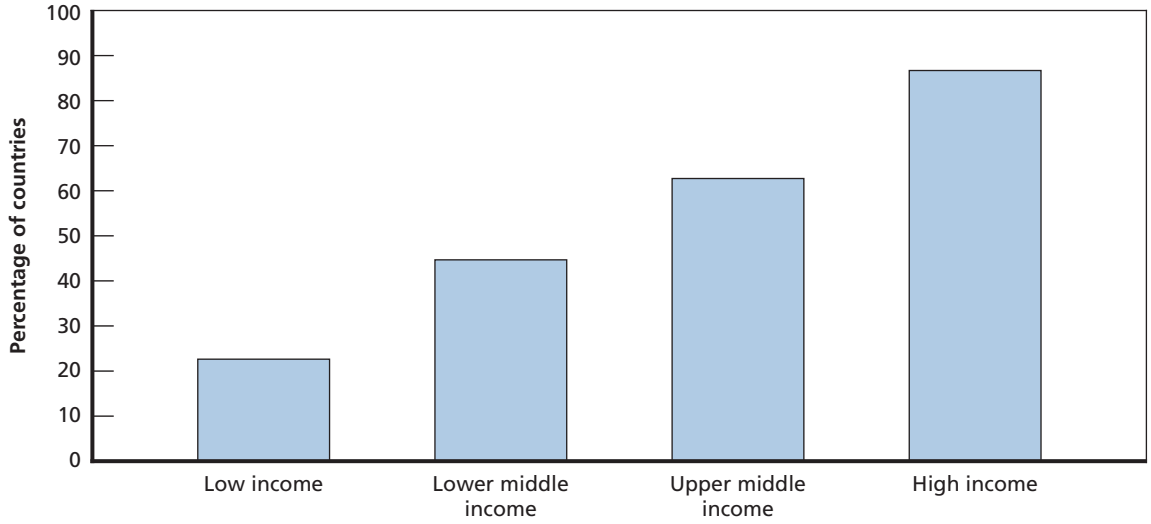
Affordability of Care

In many countries, affluent populations in urban centers have access to adequate care and medicines for NCDs and sometimes even to advanced health care facilities. In India, for example, there has been a rapid growth of private tertiary-care hospitals, which cater to the urban affluent sections and are now vying to attract international medical tourism (Reddy et al., 2005). But for poorer segments of the population, cost can create substantial obstacles to access, because care for NCDs is not always covered by health insurance or sufficiently subsidized (Wagner et al., 2011). According to the WHO's 2010 NCD country capacity survey, ***only 25 to 35 percent of low-income and lower-middle-income countries have insurance schemes, be they public or private, that cover NCD-related services and treatments***,[10] as compared with 85 percent of high-income countries (see Figure 3.3).

Limited coverage implies substantial cost sharing. Indeed, Wagner et al. (2011) found that in 51 low- and middle-income countries, health care expenditures accounted for 13 to 32 percent of total four-week household expenditures for all households. Some countries have social programs for the poorest strata of the population. For example, according to interviews we conducted with in-country policy experts, Indonesia has programs at both the federal and

[10] This does not include government-subsidized care.

Figure 3.3
Proportion of Countries in Which NCD-Related Services and Treatments Are Generally Covered by Health Insurance, by WHO Region and World Bank Income Group, 2010



SOURCE: World Health Organization, 2011a.
RAND *OP349-3.3*

the provincial levels that subsidize indigent care; India provides poor patients with social security cards, which entitle bearers to free treatment at public facilities. In addition to treatment costs, illness-related loss of productivity can severely burden households (Ait-Khaled et al., 2007) and further deteriorate households' ability to pay for necessary care.

Care Coordination Between Health Care Levels

Coordination between primary and specialty care is critical for the management of NCDs, particularly for patients at advanced stages. However, an effective referral system is lacking in many developing countries. Typically, according to providers we interviewed from several countries, notably Nigeria and Guatemala, patients visit a primary care clinic and are then referred to a hospital for further care. Unfortunately, there is little communication with the hospital and little follow-up with patients, so many patients are lost in the system. In other countries, such as the Philippines, a referral system is generally not utilized, or referrals are not feasible for patients, most of whom decide whether to visit a higher-level health facility (Higuchi, 2010).

Appropriate Diagnostic Facilities

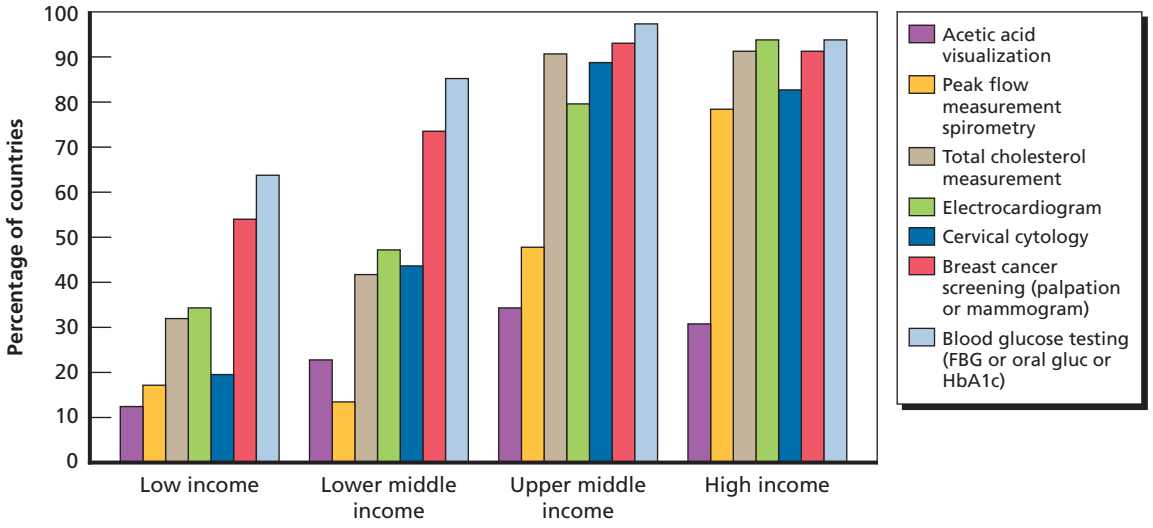
Basic technologies for diagnosing NCDs and/or tracking their treatment are commonly lacking in primary-care settings in developing countries. For example, a study conducted by the International Insulin Foundation found that only 6 percent and 25 percent of health centers in Mozambique and Zambia, respectively, could measure blood glucose levels (Beran, McCabe, and Yudkin, 2008; Beran, and Yudkin, 2006; Beran, Yudkin, and de Courten, 2005). Another study, this one looking at diabetes care in the Philippines, indicated that doctors and health workers in primary health care settings could only manage stable and uncomplicated cases

because they had limited access to equipment and medicines (Higuchi, 2010). According to an asthma expert, many health centers in developing countries do not have spirometers to diagnose and monitor asthma and COPD. Systematic data confirm these anecdotal observations: The WHO's 2010 NCD country capacity survey indicates that the ***availability of diagnostic technologies for NCD in low-income countries is about one-quarter that of high-income countries*** (see Figure 3.4).

Appropriate Treatment of Diagnosed Patients

As was discussed earlier, health care systems in developing countries have long focused on communicable diseases, maternal and child health, and injuries, and have yet to adapt to the rapidly increasing prevalence of NCDs. For example, a WHO study in ten developing countries indicates that less than one-fifth of all patients with a history of cardiovascular disease were treated with statins (compared to almost 58 percent of patients in EUROASPIRE [European Action on Secondary and Primary Prevention through Intervention to Reduce Events] II, a European-based study of established cardiovascular disease patients), and about one-tenth of patients with coronary heart disease were not on any type of medication, including aspirin or beta-blockers (Mendis et al., 2005). Similarly, in Mozambique, among patients who were aware of their hypertensive status,[11] only about half were being treated pharmacologically, and only 40 percent of treated patients were adequately controlled. Furthermore, non-pharmacological approaches to management of hypertension (e.g., lifestyle interventions such as improved diet, regular exercise, and smoking cessations, or traditional and herbal medicines) were mostly prevalent among patients who were already being treated pharmacologically (Damasceno et al., 2009).

Figure 3.4
Availability of Laboratory Tests and Basic Technologies in Primary Care



SOURCE: World Health Organization, 2011a.

RAND *OP349-3.4*

[11] Only 18.4 percent of patients in the study were aware of their hypertensive status. The authors hypothesize that this is because a high proportion of patients do not get their blood pressure measured.

A household survey conducted in a rural province of South Africa indicated that while 29 percent of patients with a chronic illness had been prescribed regular treatment, only 73 percent of them were pursuing the treatment. Additionally, among the 30 case-study households (followed over ten months) in which 34 chronic care patients were identified, only 21 of them (62 percent) received an allopathic diagnosis, and only 12 (35 percent) received regular treatment (Goudge et al., 2009).

Limited drug treatment of NCDs can be explained by a lack of provider knowledge and education. For example, robust guidelines for NCD care are lacking or are not promoted or adhered to. The WHO's 2010 NCD country capacity survey found that 53 percent of countries surveyed (n=167) had government-approved national guidelines for managing NCDs, but only 17 percent of the countries had implemented these guidelines (World Health Organization, 2011a). Indeed, according to Grimshaw, Eccles, and Tetroe (2004), failure to translate evidence-based guidelines into practice is rather common. Further, several policy experts indicated that guidelines were seldom adjusted to local requirements. For example, a number of countries used guidelines for breast cancer treatment that were directly obtained from western countries with no adaptation for differences in resources (Anderson et al., 2006).

Prescribing decisions are often not guideline based, instead depending on each provider's preferences and (as was noted by several providers and policy experts) the provider's level of interaction with the pharmaceutical industry. Indeed, the pharmaceutical industry plays an important role in informing doctors about drug treatment through detailing and sponsoring continued professional development programs (Malavige, 2004). Several of these interviewees expressed concern that the pharmaceutical industry might unduly influence prescribing decisions in the absence of independent educational programs. There is some evidence of this in the literature; for example, a study evaluating prescriptions from ten private facilities in Nigeria found that although the WHO recommends that 100 percent of medicine prescriptions be done in generic name, only 54 percent of prescriptions were for generics (Tamuno, 2011). Similarly, Enwere, Falade, and Salako (2007) found that only about half of the medicines prescribed at a teaching hospital in Ibadan, Nigeria—the College Hospital—were in generic name. Nevertheless, it is important to note that these studies do not make a direct causal link between pharmaceutical industry practices with respect to informing doctors about drug treatment and doctor-prescribing patterns. Furthermore, there is wide variability depending on the country. As a contrast to Nigeria, in neighboring Niger, a study examining prescription habits in 19 health centers in the Tahoua region found that almost 100 percent of medicines were prescribed as generics (Mallet, Njikam, and Scouflaire, 2001). Similarly, it was found that 82 percent and 94 percent of medicines prescribed, respectively, in Tanzania and Zimbabwe were generics (Hogerzeil, et al. 1993)

Usage: Is There Adequate Treatment Adherence?

Even if treatment is prescribed, patients might not adhere to their regimens. The WHO defines adherence as "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (World Health Organization, 2003). We focused on two main classes of nonadherence: non-fulfillment of medicines, and non-persistence. In the first case, providers write

prescriptions but they are never filled, and in the second case, patients take their medication irregularly or discontinue its use.

Adherence to drug treatment is an important component of managing chronic diseases. Studies have shown, for example, that adherence to statins and beta-blockers is positively associated with survival after myocardial infarction (Rasmussen, Chong, and Alter, 2007). In patients with stable coronary artery disease, adherence to beta-blockers, statins, and ACE inhibitors is correlated with a 10 to 40 percent relative decrease in risk for hospitalization and a 50 to 80 percent relative decrease in risk for mortality (Ho et al., 2008).

Low adherence rates are a universal problem. Studies have estimated that adherence rates are typically around 50 percent, even in developed countries (Haynes et al., 2002). Only limited data exist for developing countries, but adherence rates in these countries are believed to be even lower. Studies conducted in China, the Gambia, and the Seychelles show that only 43 percent, 27 percent, and 26 percent, respectively, of patients with hypertension comply with their antihypertensive drug treatment regimens (Guo, He, and Jiang, 2001; van der Sande et al., 2000; Graves, 2000).

The underlying causes of low adherence are multifactorial and include out-of-pocket cost, low levels of health literacy, the difficulty of treating asymptomatic diseases, depression, side effects of medications, and patients' lack of faith in the provider and treatment (Schneeweiss et al., 2007; Richardson, Simons-Morton, and Annegers, 1993; Ross, Walker, and MacLeod, 2004; Miller, 1997; Vermeire et al., 2001). City dwellers, as well as wealthier and more-educated patients, tend to be more adherent (Yiannakopoulou et al., 2005). Following a WHO framework, we categorized these causes into five categories for our analysis: socioeconomic and demographic, provider or health system, patient, condition, and therapy.

Socioeconomic and Demographic Factors

Cost of Medicines Relative to Income. Our review showed that most NCD medicines for first-line treatment are likely to be available in generic form and thus at low manufacturer prices. Even in the case of insulin, for which, according to a 2008 WHO report, "high costs in the private sector and low availability in the public sector were the largest barriers for poor access" in developing countries, ***manufacturer price is no longer a key issue, due to differential pricing schemes and the increasing availability of biosimilar insulin*** (Volman, 2008, p. 4). Since 2001, Novo Nordisk, the world's largest producer of insulin, has sold insulin at a price no higher than 20 percent of the average price in North America, Europe, and Japan to 49 of the world's least-developed countries (Volman, 2008).[12] And, as was mentioned above, follow-on insulins have been available for many years in the developing world (Jelkmann, 2010).

Although nearly all first-line NCD medicines are off patent, inhalers for asthma patients may constitute an exception. While the active compounds used in inhalers are no longer protected by patents, the delivery technology typically is. Patents on the delivery technology may contribute to the limited access to low-cost inhalers in the developing world (Ait-Khaled et al., 2000; Ait-Khaled et al., 2007; Niëns et al., 2010). To tackle this issue, the Asthma Drug Facility—created by the International Union Against Tuberculosis and Lung Disease and supported by the WHO—is pooling purchasing power from developing countries to procure quality-assured asthma inhalers at competitive prices (Asthma Drug Facility, 2009).

[12] Eli Lilly has recently launched a comparable initiative for the 50 least-developed countries.

While high manufacturer prices are currently not a major factor in limiting access, high cost to patients as a result of markups along the supply chain are. Bate, Tren, and Urbach (2006, p. 1), for example, claim that "import tariffs, taxes, duties and bureaucratic rules and regulations deny people medicines," and Bate et al. (2006) point to an EU study on essential medicine for communicable diseases that found that ***countries with high tariffs and taxes on pharmaceutical products (such as Nigeria, Pakistan, India, and China) were also those with low access***.

Table 3.5 illustrates the impact of cumulative markups[13] for several developing countries. The table shows that the total markup accumulated along the supply chain for a basket of 15 medicines (including six antiasthmatic, antihypertension, and antidiabetic medications) ranged from 17 to 84 percent in the public sector and from 11 to 6,894 percent in the private sector.

The data suggest that ***wholesale and retail markups account for the largest part of the difference between manufacturer prices and final cost at the point of dispensing***. Tariffs and other duties and taxes tend to be small and are often waived entirely for essential medicines. A study by the European Commission, for example, found that the average value added tax on pharmaceuticals was 8.8 percent; "other duties" amounted, on average, to 2.8 percent; and average tariffs made up just 1.9 percent in the 17 least-developed countries assessed. In total, the least-developed countries had an average rate of taxes and duties of around 14 percent. Creese (2011) found that low- and middle-income countries—if they tax medicines at all—apply tax rates of around 5 to 34 percent. Conversely, wholesale and retail markups can be considerable; in an analysis of 36 developing countries, Cameron et al. (2009) found wholesale markups of as little as 2 percent (in Pakistan) and combined import, distribution, and wholesale markups of as much as 380 percent (El Salvador). They also found retail markups ranging from 10 percent (Mongolia) to 552 percent (El Salvador). Especially in the private sector, service providers often

Table 3.5
Comparison of Public- and Private-Sector Markups

	Total Cumulative Percentage Markup	
Country	Public Sector	Private Sector
China (Shandong)	24–35	11–33
El Salvador	—	165–6,894
Ethiopia	79–83	76–148
India	—	29–694
Malaysia	19–46	65–149
Mali	77–84	87–118
Mongolia	32	68–98
Morocco	—	53–93
Uganda	30–66	100–358
Pakistan	—	28–35
Tanzania	17	56

SOURCE: Cameron et al., 2009.

[13] The sum of all markups added throughout the value chain from the manufacturer's sales price through to the final patient price.

charge significant markups, resulting in "prices that are several times higher than the international reference price"[14] (Samb et al., 2010), as shown in Table 3.6.

As a result of these markups, the effective cost of NCD medicines to patients relative to their incomes remains an important problem in low-income countries, as well as in poorer populations of the BRIC and lower-middle-income countries. The cost of a one-month course of intermediate-acting insulin, for example, corresponds to just 2.8 days' wages in Brazil, but 19.6 days' wages in Malawi (Mendis et al., 2007).

A study conducted in Ghana revealed that of the 93 percent of patients there that were noncompliant with their antihypertensive regimens, 96 percent cited cost as the main reason (Buabeng, Matowe, and Plange-Rhule, 2004). A study in Bangalore, India, reported that the majority of patients found it difficult to pay for their medicines (Reddy et al., 2005). Vertical funding that provides support only for selected medicines does nothing to diminish the high cost of NCD medicines to patients. According to a provider from a Latin America country: "The public sector does not subsidize or offer NCDs drugs as they do for infectious disease drugs. Patients use their own means to get drugs. Cost is prohibitive to compliance for the ongoing treatment of chronic diseases."

Health Literacy. As a provider from Guatemala put it, "Patients must be able to read and comprehend basic concepts and tasks related to health; with low level of literacy, health literacy is even lower." The issue of low health literacy, irrespective of overall educational levels, turns up in all developing nations, from low-income countries to the BRIC countries. Providers from

Table 3.6
Median Price Ratios of Lowest-Priced Generics to the Median International Reference Price in the Private and Public Sector, by WHO Region

	Lowest-Priced Generic	Glibenclamide 5mg capsule/tablet	Salbutamol 200-dose inhaler .1 mg/dose
Africa	Private sector	33.9	7.2
	Public sector	17.7	3.6
Americas	Private sector	67.6	5.6
	Public sector	3.2	1.8
Eastern Mediterranean	Private sector	25.1	3.3
	Public sector	18.0	3.0
Southeast Asia	Private sector	19.1	4.6
	Public sector	17.7	Not available
Western Pacific	Private sector	34.6	4.3
	Public sector	57.0	4.6

SOURCE: Cameron et al., 2009.

NOTE: Unit shown is the ratio of a medicine's median price across outlets to the Management Sciences for Health median international reference price for the year preceding the survey.

[14] International reference prices are used to compare medicine prices across countries. An example of such is the Management Sciences for Health (MSH) median international reference price, which "represent[s] actual procurement prices for medicines offered to low-income and middle-income countries by non-profit suppliers and international tender prices. Most MSH prices are for generic products and are usually ex-works prices (the price at the purchase site that does not include insurance and freight costs)" (Cameron et al., 2009, p. 3).

Guatemala and Nigeria explained: "Patients do not understand their diseases and their management," and the lack of education is a major issue in compliance with medicine regimen: "Many times patients are confused as to when, or how many drugs to take."

A health provider from Nigeria asserted: "Even with educated patients it is hard to explain the disease process; now imagine explaining it to non-educated patients!" Studies conducted in Nigeria, China, and Pakistan show that ***a patient's lack of knowledge and low health literacy had a significant negative impact on adherence to medicine regimens*** (Busari et al., 2010; Hashmi et al., 2007; Li et al., 2003.

Providers or Health-System Factors

Quality of Provider-Patient Communication. Several providers told us that they often do not have enough time to properly communicate with patients. As a provider from a lower-middle-income country tells: "The system is overcrowded, many providers are trying to get through patients, and so we do short consultations. You don't have time to communicate about problems and consequences of non-compliance in details." Indeed, Whiting, Hayes, and Unwin (2003) revealed that consultations are too short to have meaningful communication with patients. Sometimes the lack of communication stems from a language barrier, as an expert provider from Guatemala mentioned: "In Guatemala, we have a significant proportion of indigenous called the Maya people. Most of them do not speak Spanish, and the government does not provide interpreters for them." A researcher stated: "We know that most patients will not fill their prescriptions; why would you spend time explaining to them the importance of complying with treatment?"

Tools to Promote Adherence. Health care providers contended that they were not trained to communicate with patients about the importance of adherence and that they lack effective tools to do so. A Nigerian provider, for example, stated: "Private clinics have guidelines and tools available to help us . . . but I have not seen these guidelines in the public sectors."

Similarly, tools to help patients learn better health behaviors are lacking. A Nigerian oncologist said: "Sometimes speaking is not enough, pictures can say thousand words; let's show them before and after pictures of breast cancer patients who did not follow their treatment." Another researcher from India asserted that there is not enough research on ways to help patients manage their diseases with good medications-taking behavior.

Continuity of Care. Local providers and policy experts identified continuity of care as a key challenge. Providers from Guatemala and Nigeria complained about the ineffective referral system, and local policy experts for Europe and Central Asia argued that the referral system is working poorly in some of the East European countries that follow the Soviet model. Patients get lost in the system and get discouraged. The expert explained: "They have weird working hours for some laboratory tests for follow-up; if the patients do not get tested for their control of diabetes or hypertension when they show up, they usually don't show up again, especially if they are feeling fine." In Russia and other former Soviet countries, an integrated general practice model has replaced the Soviet model of primary care; despite this new model, however, some of the former Soviet countries struggle with poor quality of care and a low threshold for referrals to hospital (Rese et al., 2005; Sharbarova, 2001). This problem is exacerbated in rural areas, where few trained general practitioners work (Sharbarova, 2001).

Patient-Related Factors and/or Socio-Cognitive Factors of Patients

Patient Beliefs. "Because they have to take medications for a long period of time, possibly forever, they don't believe that the doctors prescribed them the correct medicine since their symptoms do not appear to be under control," said a doctor from Nigeria. Many breast cancer patients in Nigeria believe that they might not survive an operation, according to an oncologist. Doubting the efficacy of the medicines is a common reason for noncompliance: Dennic et al. (2011) found that 40 percent of patients in Bangalore reported not taking their medication because they believed it was not working.

At the same time, patients prefer natural or homeopathic treatments and/or visits to traditional healers, which are part of the cultural belief systems of many countries. Interviews with providers and researchers from Indonesia, India, Nigeria, and Guatemala stated that patients use alternative treatments either to complement their medicine regimen or to obtain faster results. A cross-sectional study in a teaching hospital of Delhi showed that 13 percent of diabetics were taking herbal medicines (Rai and Kishore, 2009). Another provider from Guatemala said: "Most times, the traditional healer is the first point-of-care for indigenous Guatemalan; they feel more comfortable and they can communicate with them." A Nigerian provider hypothesized: "Patients are looking to get well promptly; they don't understand the idea of chronic conditions so they look for short-cut."

Lastly, patients may simply forget to take their pills. A cross-sectional study conducted in southwestern Nigeria found that a common reason for non-compliance with drug treatment regimens was forgetfulness; in fact, forgetfulness accounted for a full 50 percent of the cases (Adisa, Aluntundu, and Fakeye, 2009). In another study, this one conducted in India on associated barriers in medication adherence, recall barrier was reported in 60 percent of cases (Dennic et al., 2011).

Social Factors. We were repeatedly told that NCD patients might not adhere because of the negative image associated with being on a long-term medicine. This is particularly problematic for cancer patients. A provider mentioned that women do not want to undergo mastectomies because of fear of stigma. Such fears may be legitimate in India, where a study found that 60 percent of patients undergoing radiotherapy were being discriminated against by their family and society (Kishore et al., 2008).

In interviews, providers from developing countries mentioned the lack of a social network in chronic disease management even though many providers are aware that social support has been shown to be crucial in improving adherence. According to an oncologist from Nigeria: "When patients see others are going through the same obstacles and find out that some are getting better, they comply because they have hope."

Depression. Depression is a well-recognized risk factor for non-adherence to drug treatment regimens. This factor has mostly been documented in developed countries (DiMatteo, Lepper, and Croghan, 2000; Wang et al., 2002). In one study of compliance with aspirin among elderly patients with coronary disease, depressive patients were significantly less likely to adhere to the regimen than were those without depression (Carney et al., 1995). Depression is also a common co-morbidity in patients with COPD and a known risk factor for non-adherence to COPD treatment. Depression is also identified as a risk factor for non-adherence to drug treatment regimens for other diseases, such as asthma (Bosley et al., 1995).

Condition Factors

"I stop taking it (medications) because I feel better," a patient told a provider. And a provider from Nigeria told us: "They are tired of taking drugs every day." Many of our experts noted that it is difficult to convince patients of the need to take medicines in the absence of symptoms, as is common in hypertension and diabetes. As one provider told us: "When they don't feel dizzy or have a headache anymore, they stop taking the pill." And a Nigerian physician said: "It is difficult to explain to my patients that no symptoms does not mean disease-free."

Therapy-Related Factors

Complexity of medicine regimens. Our interviews with providers indicate that patients get confused by the complexity of medication regimens, as co-morbidities are common among NCD patients (Chryssidis et al., 1981; Dolce et al., 1991). A study in southwestern Nigeria, for example, noted that ***the complexity of a medicine regimen was a cause of non-compliance*** in 30 percent of patients (Adisa, Aluntundu, and Fakeye, 2009). Studies find that patients on once-daily medicine are more likely to adhere to their drug treatment regimens than are patients required to take medicine multiple times a day (Claxton, Cramer, and Pierce, 2001).

Side effects. "Patients who experience side effects usually stop taking prescribed drugs," a provider from Nigeria told us. Fear of medications or actual side effects from them can interfere with adherence. In a study conducted in southwestern Nigeria, 80 percent of respondents that experienced side effects stopped taking the medications (Adisa, Aluntundu, and Fakeye, 2009).

SECTION 4

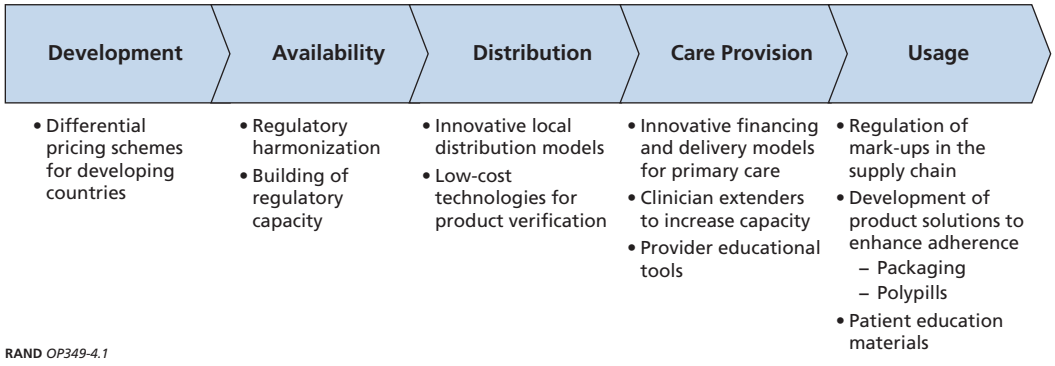
Promising Ideas for Improving Access to NCD Medicines

Through our analysis of the various obstacles to NCD medicine access, we sought to identify innovative and promising ideas, initiatives, programs, and practices that have been proposed or implemented in countries or regions of interest to overcome these obstacles. As outlined in Figure 4.1 and discussed in more detail in the subsections below, this section provides an overview of some of the best practices identified across the five dimensions of access barriers that we covered in Section 3. The ideas presented here are not meant to be exhaustive, but rather to serve as examples of promising *and* feasible—i.e., not requiring fundamental changes in available resources and governance—initiatives for improving access to NCD medicines throughout the developing world.

Development of Medicines and Delivery Technologies

For non-cancer NCDs, potent medicines used as first-line drug treatment have been developed in all critical medicine categories. At least one potent first-line medicine in each category is no longer under patent protection and is therefore likely to be available in generic form. Thus, as stated previously, ***medicine development and manufacturer prices are of lesser concern than are the other obstacle categories for improving access to NCD medicines in developing countries***. The one notable exception is inhalers for asthma and COPD patients. While the compounds used in inhalers are no longer patent protected, the medicine-delivery technology used in those inhalers is typically proprietary. To tackle the lack of access to low-cost inhalers in the devel-

Figure 4.1
Promising Ideas for Addressing Obstacles to NCD Medicine Access



oping world, the International Union Against Tuberculosis and Lung Disease, supported by the WHO, created the Asthma Drug Facility, which pools purchasing power from a wide range of developing countries to purchase high-quality asthma inhalers at competitive prices. This practice has proved effective and could be expanded with the support of the pharmaceutical industry. Alternatively, the pharmaceutical industry could consider differential pricing schemes for developing countries, a practice that has successfully reduced financial obstacles to access to insulin.

Enhancing Availability

Although it is politically often difficult to achieve, ***one promising approach for enhancing the availability of NCD medicines in developing countries is regulatory harmonization***, such as in the areas of product registration, GMP requirements, labeling requirements, and product identification codes. Greater harmonization would allow for standardized processes and procedures among pharmaceutical companies, importers, and country-level administrators around the world, creating efficiencies and economies of scale that enhance availability. Europe serves as a leading example when it comes to harmonization of product registration, with the European Medicines Agency (EMA) providing a centralized procedure for all EU countries, as well as Iceland, Liechtenstein, and Norway.[1] The 2010 evaluation of the EMA that was conducted by Ernst & Young on behalf of the European Commission (Ernst & Young et Associés, 2010) has been positive overall, and EMA has been recognized as having notably contributed to the harmonization and acceleration of registering medicinal products within the EU (Singer, 2008).

There are other regional initiatives, such as the African Medicines Registration Harmonisation initiative, which aims to a) create a collaborative network through partnership between regulatory authorities of participating countries and/or selected subregional economic blocks, b) harmonize technical requirements for the regulation of medical products and build confidence so that agreed harmonized standards are respected by participating authorities, c) establish a framework for joint evaluations of application dossiers and inspections of medicine manufacturing sites, d) strengthen the capacity for regulatory oversight, and e) develop information management systems and promote the exchange of regulatory information (World Health Organization, 2008b). However, to reach these objectives, strong political commitment is necessary to support the complex implementation process.

In the meantime, partial harmonization in such areas as GMP inspection, following models like the PIC/S,[2] could increase efficiency. The use of international GMP standards would optimize the limited resources within each regulatory authority and allow them to be redirected to other areas, such as pharmacovigilance. It would also pave the way for mutual recognition of inspections, which would alleviate the work load for the often resource-constrained regulators in the developing world.

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[1] This procedure is mandatory for biotechnology medicines; medicines for HIV/AIDS, cancer, diabetes, and neurodegenerative diseases; and orphan medicines intended for the treatment of rare diseases.

[2] PIC/S, a cooperation of nearly 40 countries in the field of GMP, aims to develop and promote harmonized GMP standards by providing guidance documents, training the respective national authorities, assessing inspectorates, and facilitating cooperation.

Significant harmonization efforts have also been undertaken by the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, which brings together European, Japanese, and U.S. regulatory and industry bodies (with the WHO, Health Canada, and the European Free Trade Association as observers) to foster harmonization of scientific and technical aspects of drug registration. Since its establishment, the ICH has developed standards for many areas, such as the common technical document (CTD), which covers all quality, safety, and efficacy information necessary for product registration and allows for harmonized electronic submission (eCTD). Almost ten years on from implementation of the CTD in the ICH regions, the benefits of the CTD for both regulators and industry are clear, with the significant amounts of saved time and resources promoting quicker access to medicine for patients.

With its Global Cooperation Group (GCG), the ICH is trying to promote collaboration in these harmonization efforts worldwide. Since its establishment in 1999, the GCG has continued to evolve to respond to the growing interest in the use of ICH harmonized guidelines from beyond the ICH regions, with much of its current focus directed toward training and capacity-building activities. ICH has invited regulators and technical experts from many countries and regions to participate in its technical working groups, thereby providing an opportunity for direct contribution to the development of the harmonized guidelines, which should help further advance the implementation of ICH guidelines beyond the ICH regions. There are also other mechanisms available for supporting resource-constrained regulators in their efforts to focus their capacities most efficiently on issues specific to their local environments (e.g., stability of medicines under local conditions and pharmacovigilance).

For example, the WHO created a CPP scheme that allows countries to rely on the registration by another recognized competent regulatory authority. The CPP ensures that the certifying country has assessed the quality, safety, and efficacy of the product. This process is especially advantageous for developing countries, where drug authorities do not necessarily always have the capacity to conduct their own evaluations. Indeed, a high proportion of countries in the developing world require a CPP as part of the registration process. However, a CPP is often required to initiate the regulatory process, which can delay access. In some countries, a more flexible approach is taken. For example, some regulatory authorities only require the CPP at the time of approval. This ensures that there is not a delay to the registration process, thus expediting medicine availability. The flexible approach is supported by the WHO and is explained on the WHO's website (World Health Organization, 2010d). Another highly valuable mechanism provided by the WHO is the Prequalification of Medicines Programme (PQP), which ensures that medicines meet acceptable standards of quality, safety, and efficacy. The PQP is increasingly used by international donors and developing countries to guide their choices when it comes to purchasing medicines (World Health Organization, 2010c).

Besides providing support by issuing CPPs and assisting the WHO in the PQP, mature national regulators have established mechanisms by which they can de facto perform an evaluation of a medication intended for use in a different country. With the intention "to provide sponsors of products for developing countries the opportunity to use the expert regulatory review services of the EMEA [now EMA] to evaluate the purity, safety, and effectiveness of a new product and to obtain a 'certificate' equivalent to a European marketing license" (Bren-

nan, 2009, p. 2), Article 58[3] was adopted. Applying this provision, EMA can evaluate a medicine that is intended exclusively for use outside the EU. This scientific evaluation is undertaken in cooperation with the WHO and follows the procedure established for marketing authorization within the EU (the only difference being that the European Commission does not issue a license; the scientific evaluation undertaken by the EMA's Committee for Medicinal Products for Human Use is the same as that used in the centralized procedure).[4] Medicines are eligible based on their use to prevent or treat diseases of major public health interest. It should be noted, however, that since Article 58 came into force in 2004, the process has been used only a handful of times. This is because most products (such as those used for NCDs) that are intended for use in the developing world are also needed in the EU. Once the applicant indicates their intention to market in the EU, they would be ineligible to use the Article 58 process.

Improvements along most of the described best practices in this section would benefit not only NCD availability, but also the availability of medication for other diseases, while in parallel freeing up resources currently tied up in duplication of scientific reviews, etc. This, in turn, may allow a stronger focus on country-specific areas, such as the specific clinical benefit/risk analysis, labeling requirements, pharmacovigilance, and pharmacoepidemiology. The WHO PQP is also trying to support capacity building in this respect; under its domain, 14 quality-control laboratories have been established so far, with 30 more (16 of which are in sub-Saharan Africa) working toward prequalification (Rägo et al., 2010).

According to a regulatory official, even high-income countries, such as Switzerland, New Zealand, and Singapore, attempt to optimize the use of their limited staff. They recognize scientific reviews if issued by stringent regulatory authorities in other countries and focus their activities on areas that benefit from local knowledge, such as pharmacovigilance. This could be a feasible model for focused capacity-building in developing countries, too.

Improving Distribution

Learning from and Partnering with the Private Sector

In particular, the consumer goods sector can offer excellent examples for setting up distribution networks that reach even the remotest areas in developing countries. A key example is the Coca-Cola Company, which has created an impressive network of local distributors on "bicycles, bullocks carts, and rickshaws,"(Hayford, Dumm, and Levine, 2011, p.10) known as manual distribution centers, to reach out to rural areas. The implementation of these centers has resulted in upwards of a 95 percent sales growth, the creation of 1,300 to 2,000 new distribution businesses, 5,300 to 8,400 new jobs, and revenues of $320 million to $520 million USD (Hayford, Dumm, and Levine, 2011). Thus, not only is distribution improved, but new opportunities to earn a livelihood are introduced.

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[3] Regulation (European Community) No. 726/2004.

[4] The outcome is, however, a "scientific opinion" rather than a marketing authorization. Nevertheless, this opinion has to be issued within the same time limit of 210 days, the only difference being that in evaluating the quality, safety, and efficacy of the medicine, EMA takes into account the appropriate benefit/risk scenarios on the populations and conditions of use as documented with clinical data by the applicant, without focusing on Europe. National experts from the regulatory agencies of the respective countries where marketing is sought are regularly invited to participate in the process and provide the local expertise.

The adoption of efficient purchasing and supply chain management practices from private industry also has promise for improving NCD medicine distribution. Fuel Africa, a medical products distributor, provides a successful example of such an endeavor. The company "reduced consumer prices for imported pharmaceuticals by 15-30 percent by streamlining its distribution model" (Hayford, Dumm, and Levine, 2011, p. 9).

Public-private partnership models, in which private partners can be companies as well as non-profit organizations, are also promising. An example is Tanzania's accredited drug dispensing outlets.[5] These privately operated outlets are organized to dispense a limited set of prescription medicines to underserved communities throughout the country. The program is designed so that independent operators need very little initial capital, and the government offers incentives and training to outlet owners. Exxon Mobil's distribution of free insecticide-treated bed nets to pregnant women and mothers at many of their petrol stations across Ghana and Zambia, and DHL's provision of refrigerated space and distribution networks for vaccines and bed nets in remote areas of Kenya (Hayford, Dumm, and Levine, 2011) are also promising partnership models that can be used as sample solutions for improving the distribution of NCD medicines.

Adopting Technologies to Enhance Safe and Effective Distribution

Major distribution improvements could be realized through the use of technology along the medicine supply chain. Such technologies as radio-frequency identification (RFID) and bar codes could be used for tracking and tracing medications, creating supply chain and inventory efficiencies, and preventing or exposing counterfeiting in the supply chain, thus enhancing patient safety. However, a key requirement for such an endeavor is adoption of an internationally or, at least, regionally accepted standard for the respective technology—e.g., bar codes, electronic data interchange, and uniform identification and codification techniques (such as RFID). The endorsement and adoption of existing standards, such as the GS1 standards (GS1, undated), may be a feasible option. The GS1 standards were developed by the global Healthcare User Group, which brings together regulatory agencies, trade organizations, and other relevant stakeholders.

The implementation of full track-and-trace technologies, however, seems far from realization—even in resource rich countries like the United States and the EU member states. Short of full traceability along the supply chain, mobile-phone-based technologies have been successfully tested to allow patients or providers to verify the authenticity of medical products. These technologies—such as MPedigree, a non-profit based in Ghana, or Sprolix's mobile-based anti-counterfeit service (provided to domestic and international pharmaceutical companies for the Nigerian market), which has already sold more than five million anti-counterfeit labels and recently received $1.8 million USD in funding from the Acumen Fund to expand its services into India and Kenya—allow end users to text a product code to a central server and receive a confirmation that the product is authentic.[6]

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[5] This is a partnership between the Tanzania Food and Drugs Authority and the Management Sciences for Health's East African Drug Seller Initiative funded by the Bill and Melinda Gates Foundation. The aim is to develop a "sustainable model for scaling up private-sector drug seller initiatives and to explore the model's transferability to another East African country" (Drug Seller Initiatives, 2011).

[6] It should, however, be reiterated that even in countries such as the United States and the EU member states, such technologies as E-pedigree systems are still in their infancy due to significant technological challenges and implementation

Technological solutions also have been piloted to improve the reliability of the supply chain. Projects such as "SMS for Life" in Tanzania and "SMS for Health" in the Gambia use mobile phone capabilities to track medicine stock levels and expiration dates for selected medicines across the supply chain, even in the most remote areas, with the goal of reducing stock-outs. The first results from "SMS for Life" were very positive, with a more than 75 percent reduction of stock-outs in one of the covered districts. It should be kept in mind, however, that better awareness and enforcement need to accompany technological innovation to achieve supply chain integrity.

Orienting Care Provision for Chronic NCDs

A number of initiatives for improving NCD care and access to NCD medicines have been proposed or are currently ongoing. The ongoing initiatives are relatively recent interventions and are being done on a small scale. Other interventions are still either at the proposal phase or the trial stage and have therefore not reported results; we cover these here because they are innovative approaches to dealing with the challenges of NCD care.

Revamping NCD Care for Different Resource Contexts

In resource-constrained environments, a priority is how to prioritize resources while providing care. To that effect, some programs are trying to integrate the management of chronic infectious diseases and NCDs. In Cambodia, Médecins Sans Frontières and the Cambodian Ministry of Health have set up a program in referral hospitals in two provincial capitals that integrates care for HIV-positive patients and patients with hypertension and diabetes. The idea behind the program is that since HIV/AIDS has attracted a significant amount of attention and funding, it presents an opportunity to also address other chronic diseases. The program employs a multidisciplinary team, including counselors, to provide patient-centered care for both types of patients using a common approach focusing on providing continuity in care, encouraging adherence to medication and lifestyle changes, providing social support, and supporting the self-management of disease. A cohort analysis of patients after 24 months of treatment indicated that while all patients had achieved satisfactory outcomes, 3 percent of HIV patients on highly active antiretroviral therapy were lost to follow-up, while a considerably higher number of diabetes and hypertension patients (29 and 32 percent, respectively) were lost to follow-up (Janssens et al., 2007). A later study indicated that the higher losses to follow-up for hypertension and diabetes might have been due to inefficacies in educational components of the program, in terms of educating patients with diabetes and hypertension about the negative consequences of non-treatment. Another factor may be that while all patients with HIV received free care, diabetes and hypertension patients were charged a fixed fee per consultation of approximately $0.50 USD (for the costs of medicines and diagnostics). These patients, as opposed to patients with HIV, also had access to alternative treatments, such as traditional medicine and pharmacies (Raguenaud et al., 2009).

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costs. A full-blown E-pedigree system would, however, make it possible to electronically document every step of a medication along the supply chain, from the manufacturer to the final point of distribution.

Further study is warranted in this area to capitalize on the tremendous resources and attention given to infectious diseases over the last decade. Indeed, there is growing discussion about how funds from the Global Fund to Fight AIDS, Tuberculosis and Malaria can be used to drive general health-system strengthening activities, which should include a focus on NCDs (Ooms et al., 2008). Whatever is done, Frenk's (2010) proposed solution for a "diagonal" approach to health care ought to be considered. A "diagonal approach" aims to bridge the divide between the vertical approach, focused on interventions for specific disease priorities, and the horizontal approach, focused on overall health-system strengthening without priority. Such an approach, similar to the approach taken in this paper, argues for explicit priorities that are used to drive improvement within the health system.

In environments where resources are less constrained, such as the BRIC countries and other emerging markets, ***some scholars are considering health care delivery systems financed through public-private partnerships involving all relevant stakeholders***, including governments, insurance schemes, pharmaceutical companies, health care professionals, and public- and private-health care providers. For example, in a recent article published in Health Affairs, Goroff and Reich (2010, p. 2208) propose a new form of "comprehensive, integrated, high-quality care, including medicines, for a specific chronic disease" in which "consultations, medicines, diagnostic tests, procedures, and therapies (would be) delivered as a package by teams of doctors, nurses, pharmacists, and other health care workers," through a "chronic disease partnership." One of the distinctive features of this partnership is that pharmaceutical companies would actively support enterprises delivering both health services and medicines, thus shifting away from the pharmaceutical companies' existing business model, which focuses on responding to the demand for medicines. While the partnership itself would be a non-profit enterprise with the sole objective of providing high-quality care, the commercial partners within the partnership could derive profit from supplying goods and/or services to the partnership. The partnership's revenues would come from direct payments from patients and from other sources, such as the public sector and social insurance schemes.

Building Capacity for NCD Care

Improving access to care and medicines for rural populations is another area in which to pursue innovations. In Ethiopia, several promising programs have been put in place to improve patient access to clinical staff in rural areas. For instance, in the rural south, the Jimma Chronic Illness Center within the Jimma University Hospital, has opened satellite health centers—each serving a population of up to 200,000 people—that are staffed with trained nurses and health officers to provide education and care to patients with chronic conditions, such as diabetes, epilepsy, and cardiac diseases. The nurses running the health centers are given periodic training in specialist care by physicians and senior nurses at the Jimma University Hospital, and senior staff from the hospital also visit the centers on a weekly basis to provide training and support (Mamo et al., 2007). A similar satellite program for diabetes exists in the northern part of the country, run by the Gondar Teaching Hospital (Alemu and Watkins, 2004)

In other places, namely South Asia, ***programs are experimenting with non-clinically trained staff to provide care and support to patients with chronic diseases***. One study conducted in India (Bangalore) and Pakistan (Islamabad) compared the abilities of non-physician health workers (NPHWs) with those of physicians in improving patients' absolute cardiovascular disease risk profile and in providing timely and appropriate referral decisions in high-risk cases. The study found over 80 percent agreement between the NPHWs and physicians; it also

found that NPHWs were able to apply the risk management package in a way comparable to that of the physicians (Abegunde et al., 2007).

Another project in India and Pakistan looks at the potential role of "care coordinators," a new category of skilled NPHWs, to promote better management of chronic diseases among patients. The project is a randomized controlled translation trial, randomly assigning patients to two groups. The intervention group has access to care coordinators, who facilitate and coordinate care and provide individualized follow-up, patient empowerment, and encouragement. In addition, these patients receive care from a multi-disciplinary team composed of a physician, dietician, social worker, educator, etc. The control group receives conventional care from the same physicians that treat the intervention group and receives the same self-management guidelines provided to patients in the intervention group. Since the program is still an ongoing trial, outcome indicators are not yet available.

A third area of innovation is in improving physician training and experience with NCDs. For example, in the Philippines, specialty education in endocrinology—needed for diabetes care—exists within medical schools and is supplemented by private nonprofit institutes that offer different courses in diabetes. Furthermore, in order to devolve diabetes care to the district level, professional associations provide training for both health professionals and other, lay members (Beran and Higuchi, 2011). One of our interviewees suggested that a similar strategy is being used in Indonesia to train primary health doctors to provide better care. There, the medical association organizes three-day training workshops for primary care providers; the workshops include courses on diagnosis, treatment for cases without complications, and referral for more-complicated cases.

Developing Adequate Guidelines for NCD Care

In recognition of the fact that there is an inadequacy of clinical care guidelines adjusted to fit many of the developing countries' health systems, a number of institutions have come together to develop some appropriate guidelines for care for specific NCDs. For breast cancer, the Breast Health Global Initiative—an international alliance of health care organizations, for-profit and non-profit organizations, and government agencies that was founded in 2002—has developed an evidence-based and resource-sensitive guideline for care with the underlying objective of enabling "a stepwise systematic approach to breast health-care improvement for limited-resource settings" (International Union Against Cancer, 2011). Effectively, these guidelines consider four basic levels of resource endowment for health systems—basic, limited, enhanced, and maximal—thus "making the guidelines simultaneously applicable to countries of differing economic capacities" (Anderson and Jakesz, 2008, p. 2578). For cervical cancer, the WHO has taken the lead in developing a similar guideline (World Health Organization and Department of Reproductive Health and Research Programme on Cancer Control, 2002). For diabetes, the International Diabetes Federation—an umbrella organization of over 200 national diabetes NGOs in 160 countries—put together a clinical guidelines task force with the objective of developing "evidence-based guidelines and clinical care recommendations which are globally and locally relevant" (Colaguiri and Colaguiri, 2011, p. 44). The resulting guideline recognizes three levels of care for diabetes (standard, minimal, and comprehensive) depending on the health care system's level of development and resources (Colaguiri and Colaguiri, 2011).

Of course, once the guidelines have been developed, the challenge of implementation remains. While some organizations, such as the International Diabetes Federation, convene regional workshops to present and explain the guidelines, there has in general been very little

attention paid to the implementation of these guidelines on a wider scale. The WHO's prioritized research agenda references a similar concern in its description of a top diabetes research priority: "[to] investigate how to identify and overcome barriers to translation of evidence-based knowledge into improved management of diabetes (medication use, technologies, health systems, culture, gender, literacy)" (Mendis and Alwan, 2011, p. 31).

Promoting Patient Adherence

Many factors impede adherence to drug treatment, and several of these factors are not particular to the developing world. Therefore, approaches for ameliorating insufficient care provision and low adherence to drug treatment should include a combination of interventions. In this subsection, we provide best practice ideas and success stories from countries attempting to increase care provision and improve adherence.

Regulating Retail Markups in the Supply Chain to Lower Medicine Costs

Wholesale and retail markups on NCD medicines are common. Such markups increase the sales price of NCD medicines to patients and discourage patient adherence to drug treatment regimens. ***Governments can play a role by regulating the markups that wholesalers and retailers can apply to medicines.*** The Malian government, for example, has been successful in containing medicine costs by fixing maximum end-user prices for wholesale and retail purchase in the private sector. A survey reveals that the prices of cardiovascular-disease-specific medicines (such as aspirin) decreased by 11 percent and that of captopril (used to treat hypertension and heart failure) decreased by 54 percent upon implementation of this program (Maiga and Williams-Jones, 2010).

According to the WHO pharmaceutical indicator survey, approximately 60 percent of low-income countries regulate the maximum wholesale or retail markups in either the public or the private sector, while as many as 90 percent of middle-income countries do so for the private retail sector (Ball, 2011). ***However, the enforcement of such markups seems rather weak, and more widespread adoption and improved enforcement are needed.***

Removing Tariffs and National Sale Taxes on Medicines

In a study by Olcay and Laing (2005), pharmaceutical tariffs for cardiovascular disease medicines in India were found to be as high as 55 percent. The same study also found that tariffs imposed on insulin containing active pharmaceutical ingredients ranged from 10 to 20 percent in Burundi, Nepal, Nigeria, Tunisia, Brazil, Paraguay, and Mexico, and above 20 percent in India. ***Taxes increase the cost of medicines and are regressive, as they target the poor disproportionately.*** Eliminating these policies makes medicines less costly to patients and thus improves adherence. A tax-elimination success story is the removal of the 10 percent standard tax by the East African Community (Kenya, Tanzania, and Uganda) in 2005 for imported prepackaged medicines.

Developing Fixed-Dose Combinations for NCDs

Fixed-dose combinations, or polypills, are combination medicines containing multiple active ingredients that are commonly used together. Currently the Single Pill to Avert Cardiovascular Events group is conducting and planning clinical trials in New Zealand, the UK, Ireland,

and Australia for the polypill manufactured by Dr. Reddy's Laboratories in Hyderabad, India. ***Polypills have the potential to lower cost for patients and to increase adherence because of their greater simplicity and convenience*** (Sanz and Fuster, 2009). Two retrospective studies, for example, have shown a 29 percent increase in drug treatment adherence in patients with hypertension using the polypill (Pan, Chernew, and Fendrick, 2008) and a 13 percent increase in treatment adherence in diabetic patients (Dickson and Plauschinat, 2008).

Developing Innovative Packaging

Prepackaging dosages of several medicines together can also help when patient recall is the main impediment to adherence. In addition, blister packs (such as are used for birth control pills) can let patients know if they have forgotten a pill. A study by Simmons, Upjohn, and Gamble (2000) on the effect of packaging in improving glycemic control and blood pressure in type 2 diabetes shows that calendar blister packaging improved metabolic control in a sample of diabetic patients in New Zealand. Another study, in Ghana, indicates that prepackaging of three-day courses of medication for malaria raised adherence from 60 to 82 percent. In addition to improving adherence, there was a reduction in the total cost of treatment and a 50 percent reduction in the time patients spent waiting at the clinic (Yeboah-Antwi et al., 2001).

Educational Programs for Patients and Counseling to Foster Collaborative Care

Patient education is an important factor in explaining low adherence, as mentioned previously. However, information given alone has been shown not to improve adherence (Vimalavathini, Agarwal, and Gitanjali, 2008) or control of glucose in diabetics (Norris, Engelgau, and Narayan, 2001). Patient education should be complemented by other interventions. Initiatives such as the patient-focused Diabetes Conversations, created by Healthy Interactions and launched by Eli Lilly and Company, can help patients with disease management while also enhancing patient interactions with health care professionals (Lilly, 2008). Heisler et al. (2002) found a significant correlation between 1) improved information given by the physician and shared decisionmaking and 2) greater patient satisfaction and adherence to treatment plans. A prospective controlled study conducted in Hong Kong showed that pharmacists' individualized counseling and follow-up on cholesterol concentrations were associated with improved medicine compliance and increased patient satisfaction (Lee, Cheung, and Chow, 2004).

Integration of Traditional Healer Services and the Formal Health System

Traditional healers play an important role in health-seeking practices in many developing nations. According to the World Bank, 80 percent of the population in Africa uses traditional medicine to help meet health care needs; in China, traditional medicine delivers 40 percent of all health care (World Bank, 2011). Given the significant presence of traditional healers in developing countries and healers' potential interference with adherence (as was mentioned by interviewees and in the literature), ***the formal health system could benefit by integrating traditional medicine into the health system and/or collaborating with traditional healers***. According to the World Bank, traditional healers have been shown to have greater influence in illnesses for which behavior change is needed (i.e., sexually transmitted diseases) because they are accepted and integrated in the community. Particularly, traditional healers can be influential in affecting the behavior of low-status and stigmatized patients. Thus, collaboration with traditional healers could also be used to improve maladaptive medication behavior in chronic illnesses. The initiative of integrating traditional healers and complementary alternative medicine

in the national health system has also received much consideration by the WHO, as seen by their traditional medicine strategy 2002–2005 (World Health Organization, 2002b).

Using Technology and Social Networks

According to a study by Adisa, Aluntundu, and Fakeye (2009), adherence among diabetics was substantially improved in patients who used simple self-help measures, such as an alarm clock, mobile phone reminders, or reminders by a family member, a practice that could be institutionalized and promoted through text messaging or other technologies.

Social networks can also contribute positively to drug treatment adherence. Having a social network has been shown to increase patient adherence to medical treatment. Stanton (1987) found in a study of hypertensives that perceived tangible and emotional support provided by others was strongly related to adherence. The results of a meta-analysis study by DiMatteo (2004) also revealed that social functioning (i.e., quality of social support) has strong effects on adherence.

SECTION 5

Implications

The key goal of our review was to help set priorities, on behalf of the research-based pharmaceutical industry, for the future policy research agenda on improving access to NCD medicines in the developing world. Like many other reviews, ours shows that NCDs present a growing challenge for developing countries and create the real possibility that gains in health made possible by better control of infectious disease and economic development are being eroded. The magnitude of these chronic diseases suggests that a robust policy response is needed. As the WHO and many other leading organizations and experts have pointed out, health promotion and disease prevention must be the cornerstones of this policy response, because improving health-related behaviors and reducing risk factors for chronic disease is the only way to reverse the underlying drivers of the NCD burden. But better prevention will take decades to achieve and will not eliminate NCDs completely, suggesting that health system capabilities must be improved in parallel. And since NCD medicines offer substantial public health gains, access to medicines is a critical component of chronic disease care.

The particular nature of NCDs means that existing paradigms for improving access to medicines do not provide sufficient answers, because these paradigms address obstacles we find to be less relevant for access to NCD medicines—namely, medicine development and manufacturer prices. Many potent NCD medicines have already been developed and will continue to be developed. This is contrasted by the experience with some communicable diseases that predominately affect developing countries, in which case individual pharmaceutical companies find it more difficult to rationalize and recoup the necessary investment in innovative medicines.

Similarly, manufacturer prices play a minor role in impeding access to NCD medicines. We found that generic alternatives are available for most first-line treatment requirements. Schemes to provide medicines at differential prices to developing countries, which are critical for maintaining access to antiretroviral medicines, are therefore less relevant for many first-line NCD medicines and exist for many NCD medicines that are still under patent protection, such as insulin and inhalers for asthma and COPD.

Our framework approach helped us to understand the complexity of removing obstacles to access to NCD medicines, and our analysis points to promising ideas to overcome those obstacles, but also illustrates that overcoming them will not be a trivial task. NCDs are the result of multiple causative factors over the course of a lifetime and require a horizontal, integrated approach to care in which the patient, family, and entire community actively participate. (World Health Organization, 2002a).

SECTION 6

Next Steps: An Invitation for Stakeholder Collaboration

Because the challenge of improving access to NCD medicines is complex, a multi-stakeholder effort will be needed to make a fundamental difference. Our goal, however, was more modest in that we were trying to set priorities for the policy research agenda of the research-based pharmaceutical industry. To this end, we focused on promising ideas that build on the industry's core capabilities and that can realistically be implemented with an industry-led effort in partnership with other stakeholders. Our analysis points to four areas for further study that emerged from our research.[1]

1. *Realizing product improvement beyond the chemical compound.* While our analysis revealed that the gains from development of additional compounds will be comparatively small, innovative ways to improve NCD medicine adherence are still dearly needed. We suggest that industry best practices be compiled in the areas of packaging, pricing, and patient education to achieve better drug treatment adherence. A particular focus should be research into the viability of fixed-dose combination products (polypills) for NCD treatment. While conceptually intuitive, the development and manufacturing of polypills are less than straightforward, because a limited range of population-adequate formulations has to be defined and produced at consistent quality. Similarly, regulatory approval may be difficult to obtain, as manufacturers would have to prove safety and efficacy of the co-administration of different compounds.
2. *Enhancing supply chain efficiency and integrity.* We observed that in contrast to what occurs with many consumer products, secure and efficient distribution of NCD medicines is far from guaranteed in developing countries. Availability in poor and remote areas remains limited, hefty markups along the supply chain are common, and the share of counterfeited product is substantial. At the same time, our review points to several creative ideas that should be studied further. A specific area of research could be an assessment of policy options for improving supply chain integrity—for example, a comparison of the potential impact of a public-sector solution to improve supply chain integrity for all medical products with a private-sector approach to marketing medicines, whose value proposition is the security of the supply chain and ability to verify product authenticity.
3. *Achieving gains from regulatory harmonization.* Although potent NCD medicines exist, their availability in developing countries can be hampered by regulatory obstacles.

[1] Given that effective medicines for NCD treatments already exist and the research-based pharmaceutical industry continues to focus on new product development, we are not advocating for additional research into promising ideas for compound development to address NCDs.

Uncertain timelines and variable requirements for product registration, GMP inspections, labeling, and product identification codes can increase cost, sometimes to a level that makes product registration prohibitively difficult in a country. Many regional initiatives aim at achieving greater harmonization of regulatory requirements that would allow for increased availability. A logical next step would be to quantify the benefits from regulatory harmonization to promote a data-driven dialog with national authorities, and to promote the optimal use of such available schemes as the WHO CPP scheme, PIC/S and the ICH GCG scheme.

4. *Improving access to primary care.* We found consistent evidence that limited access to quality primary care is the key obstacle to improving NCD drug treatment. In the absence of a robust primary care system, NCDs go unnoticed until complications arise, adequate treatment is not initiated, treatment effect is not consistently monitored and terminally ill patients do not receive palliative care. At the same time, improving access to primary care is a complex challenge requiring that such fundamental issues as resourcing, governance, and capacity building be addressed. As an initial step, we propose a survey of innovative approaches for delivering effective and efficient primary care in developing countries and an assessment of which of those approaches can be scaled up in which contexts. Our initial review points to several promising ideas to which an in-depth review could add.

We are confident that further research into these priority areas can yield actionable guidance on how to improve access to NCD medicines in the developing world and that the research-based pharmaceutical industry is committed to executing this program. While far from resolving the fundamental issues of preventing and treating NCDs, the evidence generated by this program will allow the industry, in partnership with other stakeholders, to contribute meaningfully to the global efforts to reduce the NCD burden. The UN high-level meeting on NCDs will generate awareness and can galvanize decisionmakers to address the issue. From this can come an opportunity to make sustainable progress, if the attention around the meeting is leveraged to engage all stakeholders in a constructive dialog. Providing evidence-based concrete steps that can be taken in the short run is critical for generating momentum and moving the agenda forward.

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