Advancing the responsible use of medicines

Applying levers for change
This report was prepared for the Ministers Summit organized by the Dutch Ministry of Health, Welfare and Sport on the 3rd of October 2012 with the theme: 

*The benefits of responsible use of medicines: Setting policies for better and cost-effective healthcare.*

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Executive summary

The IMS Institute for Healthcare Informatics has identified an opportunity to save a half trillion dollars in annual global health spending through the responsible use of medicines. Responsible medicine use by health system stakeholders—namely policymakers, payers, clinicians, nurses, pharmacists, and patients—would ensure that their capabilities, resources and activities are aligned so that patients receive and use the right medicines at the right time. In today’s economic climate, this should be a top health policy priority, given both the positive impact on overall spending and the resulting improvement in health outcomes.

Ministers of Health and other health system leaders should identify and prioritise improvements in medicine use to realise this opportunity. There are six levers driving the greatest inefficiencies in the health system. These levers include: patient nonadherence, untimely medicine use, antibiotic misuse and overuse, medication errors, suboptimal generic use, and mismanaged polypharmacy. Other important levers are the misuse of expensive therapies, suboptimal supply management, and medicine abuse by patients.

This technical report offers five primary recommendations that Ministers of Health and other health system leaders can implement to drive improvement. Based on primary and secondary research, the recommendations focus on areas where Ministers can have the greatest influence:

- Strengthening the role of the pharmacist in medicines management.
- Using medical audits focused on elderly patients to manage polypharmacy.
- Implementing mandatory reporting of antibiotic use by providers.
- Encouraging behaviour change among healthcare professionals to support error and problem reporting.
- Supporting targeted disease management programmes for high-risk patients with chronic diseases to ensure timely therapy initiation.

The feasibility of these recommendations varies by country and a Minister’s corresponding spheres of influence to drive change. Successful implementation depends on a blend of: policies to trigger improvements in medicine use; stakeholder collaboration; education of health professionals and patients; availability of health informatics for informed decision making; and alignment of incentives to optimise clinical and/or dispensing practices.
All health system leaders, regardless of country financing or income level, can improve the use of medicines. While the challenge may appear overwhelming, it is possible to identify starting points and work incrementally towards improvement. Against the backdrop of uncertainty in the healthcare sector, perfect cannot stand in the way of the good. Change is possible, and outcomes can and should be improved. In fact, Ministers of Health can make this happen within a typical political tenure—and realise the benefits.

Harnessing the power of information can prioritise interventions, monitor progress via process and health outcomes indicators, and support behaviour changes among healthcare stakeholders and patients. Anecdotal evidence only goes so far in authenticating the need for policy change. Real-world evidence is crucial, and that is where health informatics can play an important role. Data collection mechanisms and analytics systems can serve as the foundation for policy change. However, as they are developed, challenges such as patient privacy, centralised vs. fragmented collection systems, and data interoperability must be considered.

In order to supplement existing sparse data, the IMS Institute developed a modelling approach to identify the half-trillion dollar opportunity across 186 countries. The methodology is based on insights from research about the drivers of country variation in suboptimal medicine use. No one factor, such as income, determines suboptimal medicine use. Instead, there is a combination of factors, including health system infrastructure, affordability, population demographics, noncommunicable disease risk factors, and medicine intensity. The analysis draws from the World Health Organization (WHO), the World Bank, the Organisation for Economic Co-operation and Development (OECD), and IMS data sources.

Health system leaders, healthcare professionals, and patients can all apply these insights to confront and resolve medicine use challenges. Budget silos can be broken down and reassessed, along with the barriers that exist today between healthcare professionals and patients. Additionally, professionals across all care settings must work together to ensure appropriate prescribing, dispensing, and monitoring of patient behaviours and outcomes. Finally, health system leaders will need to adopt a patient-centric approach and rethink how care is coordinated in light of ageing populations and the increase in noncommunicable and chronic disease burdens.

These insights are intended not only to ignite discussion and debate among Ministers of Health, but also to provide the impetus for immediate action in collaboration with champions of healthcare—professionals and patients alike.

Murray Aitken and Lyudmila Gorokhovich
IMS Institute for Healthcare Informatics
Preface

Improving the responsible use of medicine is an urgent health policy priority. Better medicine use can improve health outcomes and alter the way health systems operate to optimise overall spending. When suboptimal medicine use occurs, resources in healthcare and medicine budgets are spent unnecessarily, and health system productivity is weakened. Consequently, it is important that all health system leaders understand the complex link between medicine and nonmedicine spending. While long-term and inpatient care constitute a considerably greater portion of total health expenditures compared with medicine use, much of that spending is driven by adverse events that stem from avoidable, medicine-use related activities.

This report examines key areas where medicine use can be assessed and addressed, but it is not intended to be an exhaustive presentation on the subject of healthcare challenges. Since health policy leaders cannot address all challenges at once, they must by selective given their country context. This report suggests three key principles to guide Ministers as they think about how to meaningfully digest the implications and identify their starting point:

1. Recognise that perfect should not stand in the way of the good.

2. Start small to build confidence that new approaches can achieve results.

3. Appreciate that healthcare is dynamic; health policy decision making always entails a degree of uncertainty.

Acquiring scientific understanding, identifying appropriate treatment guidelines, providing patient options, and evaluating evidence for what does and does not work is an evolving process.

The recommendations and analysis presented in this report are gleaned from a breadth of primary and secondary research as well as external input and IMS review. Nineteen distinct country case studies and supporting evidence from more than 30 countries form the backbone of this analysis. While the final recommendations are specifically designed for Ministers of Health, the bulk of this report is equally relevant to other health system leaders in different geographic and clinical settings. With more than 50 recommendations across 10 different areas of opportunity, every reader will find relevant nuggets of meaningful information.

The structure of this report centres on the quantified opportunity. The chapters cover six primary levers, three secondary levers, and have a focus on health informatics, one of the most critical capabilities health system leaders can strengthen to realise improvements. Each chapter provides:

- A snapshot of the quantified opportunity across a selection of countries based on those invited to participate at the Ministers Summit on The Responsible Use of Medicines.
- A list of recommendations accompanied by three criteria: time to impact, level of health outcome improvement, and necessary spend.
- An in-depth overview of the basis for the recommendations.
- Country-level case studies to demonstrate how change is possible.
- Background analysis.

There is still much information that is not captured or tracked, possibly fuelling the likelihood of underestimation across the board. More importantly, this is only the beginning of revisiting medicine use to drive improvements in outcomes, costs, and livelihoods across health systems.
Acknowledgements

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# Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABDA</td>
<td>Federal Union of German Associations of Pharmacists</td>
</tr>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme (ACE)-inhibitors</td>
</tr>
<tr>
<td>ADHD</td>
<td>Attention-deficit hyperactivity disorder</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse drug reaction</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse drug event</td>
</tr>
<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>AMR</td>
<td>Antimicrobial resistance</td>
</tr>
<tr>
<td>ANMOG</td>
<td>German healthcare reform (Arzneimittelmarkt-Neuordnungsgesetz – Germany)</td>
</tr>
<tr>
<td>ANVISA</td>
<td>National Agency of Health Surveillance (Brazil)</td>
</tr>
<tr>
<td>APR</td>
<td>Antibiotic prescribing rate</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin II receptor blocker</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>ASHP</td>
<td>American Society of Health-System Pharmacists</td>
</tr>
<tr>
<td>BASCAP</td>
<td>Business Action to Stop Counterfeiting and Piracy</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CAM</td>
<td>Complementary and Alternative Medicine</td>
</tr>
<tr>
<td>CBIA</td>
<td>Community-Based Intervention Association</td>
</tr>
<tr>
<td>CBP</td>
<td>Calendar blister packaging</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CDS</td>
<td>Clinical Decision Support system</td>
</tr>
<tr>
<td>CEE</td>
<td>Central and Eastern Europe</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>CNAMTS</td>
<td>French National Health Insurance Agency (Caisse Nationale d’Assurance Maladie)</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CPOE</td>
<td>Computerised Physician Order Entry system</td>
</tr>
<tr>
<td>CRF-SP</td>
<td>Regional Council of Pharmacy of São Paulo (Brazil)</td>
</tr>
<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>DAWN</td>
<td>Diabetes Attitudes, Wishes, and Needs Study</td>
</tr>
<tr>
<td>DAWN</td>
<td>Drug Abuse Warning Network</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>DMP</td>
<td>Diabetes management programme</td>
</tr>
<tr>
<td>DOTS</td>
<td>Directly observed treatment short course</td>
</tr>
<tr>
<td>DRG</td>
<td>Diagnostic Related Group</td>
</tr>
<tr>
<td>DTC</td>
<td>Direct-to-consumer</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency department</td>
</tr>
<tr>
<td>EFPIA</td>
<td>European Federation of Pharmaceutical Industries and Associations</td>
</tr>
<tr>
<td>EHR</td>
<td>Electronic health record</td>
</tr>
<tr>
<td>ESAC</td>
<td>European Surveillance of Antibiotic Consumption</td>
</tr>
<tr>
<td>ESAR</td>
<td>European Surveillance of Antibiotic Resistance</td>
</tr>
<tr>
<td>eTP</td>
<td>Electronic transfer of prescriptions</td>
</tr>
<tr>
<td>FIP</td>
<td>International Pharmaceutical Federation</td>
</tr>
<tr>
<td>GDP</td>
<td>Gross domestic product</td>
</tr>
<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>HAP</td>
<td>Health Alliance Plan (Denmark)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Glycated haemoglobin</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Hepatitis B surface antigen</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HPA</td>
<td>Health Protection Agency (UK)</td>
</tr>
<tr>
<td>HTA</td>
<td>Health Technology Assessment</td>
</tr>
<tr>
<td>ICS</td>
<td>Inhaled corticosteroids</td>
</tr>
<tr>
<td>INN</td>
<td>International Nonproprietary Name</td>
</tr>
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</table>
### Acronyms continued

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>KBV</td>
<td>Federal Association of Statutory Health Insurance Physicians (Kassenärztliche Vereinigungen - Germany)</td>
</tr>
<tr>
<td>MCA</td>
<td>Multicompartment compliance aids</td>
</tr>
<tr>
<td>mCRC</td>
<td>Metastatic colorectal cancer</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>Multidrug-resistant tuberculosis</td>
</tr>
<tr>
<td>MEMS</td>
<td>Medication Event Monitoring System</td>
</tr>
<tr>
<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency (UK)</td>
</tr>
<tr>
<td>MoH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>MPR</td>
<td>Medication Possession Ratio</td>
</tr>
<tr>
<td>MRSA</td>
<td>Methicillin-resistant Staphylococcus aureus</td>
</tr>
<tr>
<td>MUR</td>
<td>Medicines Use Review</td>
</tr>
<tr>
<td>NARMS</td>
<td>National Antimicrobial Resistance Monitoring System (US)</td>
</tr>
<tr>
<td>NCDs</td>
<td>Noncommunicable diseases</td>
</tr>
<tr>
<td>NHSO</td>
<td>National Health Security Office (Thailand)</td>
</tr>
<tr>
<td>NIVEL</td>
<td>Netherlands Institute for Health Services Research</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Non-small-cell lung cancer</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisaton for Economic Co-operation and Development</td>
</tr>
<tr>
<td>OOP</td>
<td>Out-of-pocket</td>
</tr>
<tr>
<td>OTC</td>
<td>Over-the-counter</td>
</tr>
<tr>
<td>PCMH</td>
<td>Patient-Centred Medical Home</td>
</tr>
<tr>
<td>PCNE</td>
<td>Pharmaceutical Care Network Europe</td>
</tr>
<tr>
<td>PCPCC</td>
<td>Patient Centered Primary Care Collaborative</td>
</tr>
<tr>
<td>PES</td>
<td>Prescription Exchange Service (Australia)</td>
</tr>
<tr>
<td>PKI</td>
<td>Public Key Infrastructure</td>
</tr>
<tr>
<td>PMR</td>
<td>Patient medication records</td>
</tr>
<tr>
<td>PNCT</td>
<td>Programme for Tuberculosis Control (Programa Nacional de Controle da Tuberculose - Brazil)</td>
</tr>
<tr>
<td>PSI</td>
<td>Pharmaceutical Security Institute</td>
</tr>
<tr>
<td>PSNC</td>
<td>Pharmaceutical Services Negotiating Committee (UK)</td>
</tr>
<tr>
<td>PTC</td>
<td>Pharmacotherapy Centre (Sweden)</td>
</tr>
<tr>
<td>SAE</td>
<td>Specialised Care Services (Brazil)</td>
</tr>
<tr>
<td>SGB V</td>
<td>German Social Code Book V</td>
</tr>
<tr>
<td>SU</td>
<td>Standard unit</td>
</tr>
<tr>
<td>THE</td>
<td>Total health expenditure</td>
</tr>
<tr>
<td>UNAIDS</td>
<td>Joint United Nations Programme on HIV/AIDS</td>
</tr>
<tr>
<td>US DHHS</td>
<td>United States Department of Health and Human Services</td>
</tr>
<tr>
<td>US FDA</td>
<td>US Food and Drug Administration</td>
</tr>
<tr>
<td>VA</td>
<td>US Department of Veterans Affairs</td>
</tr>
<tr>
<td>WHA</td>
<td>World Health Assembly</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>Extensively drug-resistant tuberculosis</td>
</tr>
</tbody>
</table>
I. The case for better use of medicines

Report focus rationale

*Revisiting medicine use is timely in light of rising healthcare costs and ample evidence that a large missed potential exists in the way medicines are used.*
1. THE CASE FOR BETTER USE OF MEDICINES

Report focus rationale

In the past decades, medicines have had an unprecedented positive effect on health, leading to reduced mortality, lowered disease burden, and consequently to improved quality of life. At the same time, there is ample evidence that a large ‘missed potential’ exists in the way in which medicines are used. The right medicine does not always reach the right patient; approximately 50% of all patients fail to take their medicines correctly (WHO 2003). Also, in many cases the capabilities of the system are not sufficient to support optimal medicines use. Important value can be gained by using medicines more responsibly. This value cannot only be expressed in terms of health gains; lost value also has important cost implications.

Given the importance of medicines use, the Dutch Ministry of Health, Welfare and Sport, in the context of the International Pharmaceutical Federation (FIP) Centennial, has decided to organise a Ministers Summit in October 2012 with the theme, “The benefits of responsible use of medicines.” The purpose of this Summit is to explore solutions to improve patient outcomes and support sustainable and cost-effective healthcare.

From analyses conducted for the Summit, significant healthcare costs can be avoided if we utilise available medicines in a more appropriate fashion. Existing estimates focusing on direct healthcare costs, such as reduction in unnecessary hospitalisations, undervalue the total cost avoidable through a more responsible use of medicines. Total avoidable costs to society are higher if productivity losses also are taken into account.

This report is one of two that the Dutch Ministry of Health, Welfare and Sport has commissioned to fuel discussions at the Summit; one from WHO and the other from the IMS Institute for Healthcare Informatics. The primary difference between the two reports is that the WHO report uses case histories to glean policy lessons from WHO experiences in low- and middle-income countries, while the IMS Institute report focuses on the avoidable cost quantification, case studies, and supporting evidence from low-, middle-, and high-income countries. Readers are encouraged to consult the briefing paper, which further describes the context of the Summit, reflects the main findings of both reports, and identifies a potential way forward.

What is meant by the responsible use of medicines?

The term ‘responsible use of medicines’ implies that the activities, capabilities, and existing resources of health system stakeholders are aligned to ensure patients receive the right medicines at the right time, use them appropriately, and benefit from them.

This description complements the WHO definition of rational medicine use:

“Medicine use is rational (appropriate, proper, correct) when patients receive the appropriate medicines, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost both to them and the community. Irrational (inappropriate, improper, incorrect) use of medicines is when one or more of these conditions are not met.”


This description incorporates the importance of stakeholder responsibility and recognises the challenge of finite resources. Conversely, suboptimal use is the exact opposite of what is meant throughout this report.

The focus of the Summit is on how to recapture lost value of medicines due to suboptimal use. Value of medicines can be gained if medicines are:

1. Matched to the right patient at the right time.
2. Taken appropriately by the patient.
3. Used within the right capabilities.

The framework explicitly does not delve deeply into topics such as innovation policies, pricing, and financing challenges. These and other issues are critical for universal medicine access, as expressed in the 2005 WHA Resolution 58.33 (World Health Assembly 2005).
Health systems aim to bring high-quality healthcare to their citizens at an acceptable cost. Health system leaders make different decisions to optimise scarce resources, often in light of political-economic interests. In some countries, high debt and fiscal deficits have placed healthcare reform high on policy agendas, with medicines as a specific priority.

In other countries such as Thailand, health technology assessments have been introduced to assist with the implementation of universal healthcare coverage.

Use of medicines is a critical factor in health system efficiency. On the one hand, medicine spending in some countries accounts for a fifth or more of all health spending. On the other, medicines also have indirectly contributed to efficient health system functioning by being a relatively cost-effective means of prevention or avoidance of costlier and more severe conditions (e.g., vaccines, statins in cardiovascular disease). Unfortunately, medicines are often overused (e.g., antibiotics) or underused (e.g., due to nonadherence). This results in avoidable adverse events, worse quality of life, and inferior health outcomes.
Revisiting medicine use is timely given rising healthcare costs and the impact the use of medicines can have to control health system costs and improve health outcomes.

Total health expenditures are rising more rapidly than incomes across high-, middle-, and low-income countries. Across high- and middle-income OECD countries, health spending per capita has surpassed economic growth since 2000. There is little reason to think this might change as emerging markets accumulate wealth and access to healthcare increases. However, the medicines market will slow down and change. While global spending on medicines is predicted to reach nearly 1.2Tn USD by 2016, this reflects a slowing growth rate of 3% to 6% over the next five-year period vs. an annual growth rate of 6.1% over the last 5 years (IMS 2012).

A closer look at health spending trends over the last decade reveals the rise in health spending combined with the inherent link between medicine use and overall health (both costs and outcomes). This begs for a reflection on whether medicine use can be improved for the benefit of the entire health system.

This concept is particularly relevant as medicine access increases in low-income countries and the trend of the last 10 years continues. In fact, emerging markets are expected to surpass the European Union 5 (EU 5) (France, Germany, the UK, Italy, and Spain) in terms of global spending, and will account for 30% of global spending on medicines in 2016 (vs. 13% for the EU 5) (IMS 2012).
A range of factors drives these trends: demographic shifts, changes in disease epidemiology, innovation, and structural health system components such as stakeholder incentive alignment. Health system leaders confront unprecedented challenges in light of an ageing population, increasing noncommunicable disease burden, and rapidly evolving science and technology. These challenges are a mirror image of opportunities. Countries are positioned better than ever to leverage information for evidence-based decision making and to learn from one another on a variety of issues, from innovative payment schemes such as performance-based reimbursement to human resource changes such as task-shifting via nurses and pharmacists.

At the core of the discussion is the patient, seen as a partner in the treatment of his or her disease. This approach affords tremendous possibilities for patients to influence treatment availability and selection in order to make the best use of medicines.

**IN LOW INCOME COUNTRIES, ALTHOUGH MEDICINE SPENDING IS A LARGER SHARE OF TOTAL HEALTH SPENDING, IT HAS BEEN OUTPACED BY NONMEDICINE SPENDING**

<table>
<thead>
<tr>
<th>Year</th>
<th>Medicine spending per capita</th>
<th>Nonmedicine spending per capita*</th>
<th>Nonmedicine spending vs. medicine spending per capita in low income countries, Average, US$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>28</td>
<td>70%</td>
<td>30%</td>
</tr>
<tr>
<td>2006</td>
<td>34</td>
<td>73%</td>
<td>27%</td>
</tr>
<tr>
<td>2007</td>
<td>39</td>
<td>71%</td>
<td>29%</td>
</tr>
<tr>
<td>2008</td>
<td>48</td>
<td>71%</td>
<td>29%</td>
</tr>
<tr>
<td>2009</td>
<td>48</td>
<td>71%</td>
<td>29%</td>
</tr>
</tbody>
</table>

*Nonmedicine spending is calculated by subtracting pharmaceutical expenditure from total health expenditure per capita.

Sources: IMS Institute for Healthcare Informatics, 2012; World Bank; WHO (latest available data for a subset of countries representing over 50% of each income group based on World Bank income groupings).
References


II. Framing the approach and quantifying the opportunity

Understanding the context and the magnitude of opportunity

Our research estimates that about 8% of total healthcare expenditure or about 500Bn USD per year globally, can be avoided with optimized use of medicines.
II. FRAMING THE APPROACH AND QUANTIFYING THE OPPORTUNITY

Framing the approach

This report focuses on three key areas as identified by the Dutch Ministry of Health, Welfare and Sport:

1 Right medicines to the right patient at the right time: A supply-side perspective that analyses how appropriate medicine use can fail if the supply process is not responsible in supporting medicine use. Issues include: suboptimal supply management, timely medicine use, medication errors, and suboptimal prescribing practices.

2 Patient usage: A demand-side perspective that analyses the issues and levers preventing the patient from using medication appropriately. Issues include: nonadherence and medicines abuse.

3 Capabilities necessary to implement the recommendations that will realise the benefits. The area of focus is related to health informatics, which fundamentally underpins all the areas covered in this report. Health informatics includes an analysis of how data collection and relevant analytics are needed to inform decision making across healthcare stakeholders to improve medicine use.

LEVERS TO ENSURE MEDICINES ARE DELIVERED TO THE RIGHT PATIENTS AT THE RIGHT TIME (1/2)

<table>
<thead>
<tr>
<th>LEVER TO REALIZE GAINS</th>
<th>RELEVANCE AND SCOPE FOR THIS REPORT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimise supply disruptions</td>
<td>Medicines shortages: Suppliers are unable to meet the demand for medicines, causing a disruption in patients’ ability to use the right medicines at the right time. Substandard medicines: Counterfeits, falsified, and/or spurious medicines that do not work appropriately in patients and/or delay quality treatment, potentially leading to adverse drug events.</td>
</tr>
<tr>
<td>Ensure timely medicine use</td>
<td>Untimely medicine use occurs when patients do not obtain medicines at the right time, leading to avoidable, relatively expensive complications downstream. This is particularly the case in specific diseases such as hepatitis B, hepatitis C, and diabetes type 2, the foci of this report. Timely medicine use prevents relatively costlier events later on, saving the health system funds and improving health outcomes.</td>
</tr>
<tr>
<td>Prevent medication errors</td>
<td>Medication errors can occur along four processes of medicine delivery 1) Inappropriate prescribing can lead to potentially severe and costly adverse impact; 2) Preparing and dispensing which is traditionally done by pharmacists and has a chance for error when the wrong dose is dispensed; 3) Errors during administration of the pharmaceutical product can occur in the following examples: administering the patient the incorrect dose of a particular drug; administering the incorrect medicine; administering the medicine via the incorrect route; 4) Errors during monitoring occur when clinicians and/or pharmacists obtain and evaluate clinical indicators and other relevant information to determine a medicine’s effect on an individual patient. Examples of errors associated with monitoring include wrong blood test results written in physician notes.</td>
</tr>
</tbody>
</table>
These key areas are not proclaimed to be exhaustive nor completely distinct from one another. Nevertheless, they provide a starting point for understanding the building blocks of inefficient medicine use that drive overuse/underuse/misuse of medicines, and consequently avoidable hospitalisations and other nonmedicine resource use. Governments can use these levers to identify:

- Which drivers of improvements in medicine use can occur in their country.
- Prioritised levers that drive the greatest inefficiencies in the system.
- Interventions towards different stakeholders in the health system to recoup avoidable costs and improve health outcomes.

The tables on these pages provide explicit definitions for each of the identified issues and levers.

LEVERS TO ENSURE MEDICINES ARE DELIVERED TO THE RIGHT PATIENTS AT THE RIGHT TIME (2/2)

<table>
<thead>
<tr>
<th>LEVER TO REALIZE GAINS</th>
<th>RELEVANCE AND SCOPE FOR THIS REPORT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manage polypharmacy</td>
<td>Polypharmacy occurs when patients take multiple medicines concurrently. Mismanaged polypharmacy leads to adverse drug events, which can be severe and costly to treat. The risk of adverse events and subsequent hospitalizations, including use of additional medicines, increases when patients are concurrently taking more than 5 medicines.</td>
</tr>
<tr>
<td>Use low-cost generics where available</td>
<td>The opportunity from safe, low-cost generics may be underexploited depending on price and volume differences between off-patent and never protected medicines. The mix of these medicines can be adjusted to reduce health system costs, provided health outcomes are not undermined.</td>
</tr>
<tr>
<td>Optimise antibiotic use</td>
<td>Antibiotics are commonly misused in terms of being overused and in rarer occasions, underused. Their availability, low price and perception by many that they can treat any kind infection lead to a high propensity of misuse and overuse. For example, they are commonly misused for viral infections. Misuse and/or overuse results in downstream avoidable costs through hospitalizations and more expensive treatment.</td>
</tr>
<tr>
<td>Use expensive therapies selectively through predictive diagnostics</td>
<td>This lever is more relevant in countries with increasing access to innovative and expensive therapies in disease areas such as oncology. In this context, it is increasingly important to ensure expensive medicines are not provided to patients who will not respond or are ineligible. Personalised medicine and predictive diagnostics can be used to identify such patients with breast and colorectal cancer. On the other hand, identifying patients who will respond to maximize the value of expensive therapies is equally important. Techniques are available in non-small-cell-lung cancer and malignant melanomas. Given the recent advent of this field, the analysis on this lever addresses recommendations and focuses on the challenges to policymakers as personalised medicine expands.</td>
</tr>
</tbody>
</table>

THE BENEFITS OF RESPONSIBLE USE OF MEDICINES • 19
LEVERS TO ENSURE PATIENTS USE MEDICINES APPROPRIATELY

<table>
<thead>
<tr>
<th>LEVER TO REALIZE GAINS</th>
<th>RELEVANCE AND SCOPE FOR THIS REPORT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase adherence</td>
<td>Nonadherence occurs when patients do not take their medicines appropriately or at all. Nonadherence is driven by a variety of factors in combination rather than in silo. These include lack of affordability, unintended patient-related factors such as forgetfulness, an unsupportive patient and healthcare professional relationship and inappropriate patient-product suitability such as packaging/device, complexity of medication regimen and adverse medication reactions. All affect patient responsiveness and medicine use. Nonadherence results in costly complications which are often more expensive than medicines and worsen health outcomes.</td>
</tr>
<tr>
<td>Reduce medicine abuse</td>
<td>Prescription abuse occurs when legal medicines are taken by patients for a purpose different from their intended prescription use. Patients also abuse over-the-counter (OTC) medicines through overdose and/or addiction. In these situations, patients are not taking the right medicines, contributing to avoidable adverse events and costs.</td>
</tr>
</tbody>
</table>

The following topics are explicitly not covered in this report:

- **Financing and health coverage-related topics**: Including the use of health technology assessments, cost-effectiveness and/or cost-benefit analyses, essential medicines lists, universal healthcare coverage and access.
- **Preventative medicine**: Vaccines and other public health interventions related to tobacco and alcohol use.
- **Quality of care**: Ensuring the patient journey in the health system is appropriate and leads to improved health quality outcomes.
- **Supply chain management**: Regulation to ensure manufacturers supply optimal medicines from a quality perspective.
- **Disease-specific approach**: The issues covered in the report are relevant to all diseases, with a focus on noncommunicable diseases (NCDs); given that people increasingly have multiple NCDs, a disease-specific analysis is unlikely to be meaningful.
- **Tension between a market-driven world and cost containment**: Although the report alludes to this topic in some areas, this area is not fully covered.

While the report does not go into these issues in depth, their crosscutting importance is recognised as relevant to Ministers of Health.
A quantified opportunity presents itself from a cost avoidance perspective with implications for improvement in health outcomes. This research estimates that about 8% of total health expenditure, or about 500Bn USD per year globally, can be avoided with optimized use of medicines, which would prevent avoidable hospitalisations and improve medicine use.

The following analysis summarises the global impact of suboptimal medicine use for 186 countries. It is indicative of where the greatest losses are and where benefits can be gained. It also is meant to be interpreted in the context of allocative and technical efficiency, not actual monetary savings.

In light of the potential for under-reporting and limited availability of data analysis in many countries, the IMS Institute suggests that the actual dollar number is between 301Bn and 650Bn USD in 2011 values. This equates to ~5% and ~11% of global health spending in 2011.

The quantification of cost avoidance and the research substantiating this analysis implies that the better use of medicines can significantly improve quality of life through reduced hospitalisations and improved health outcomes such as morbidity and mortality. Patients’ ability to live longer and enjoy a better quality of life contributes to a country’s overall well-being and economic productivity.

ABOUT $500BN DOLLARS MAY BE AVOIDED THROUGH BETTER RESPONSIBLE MEDICINE USE

Source: IMS Institute for Healthcare Informatics, 2012. Please see Methodology section for details on quantification. This includes 186 countries.
III. Synthesised recommendations for Ministers of Health: Outcomes and analysis

What can ministers do?

All health system leaders - regardless of country, financing or income level - can improve the use of medicines.
III. SYNTHESISED RECOMMENDATIONS FOR MINISTERS OF HEALTH: OUTCOMES AND ANALYSIS

Synthesis: What can ministers do?

The IMS Institute's recommendations focus on six specific levers that can reduce nonmedicine spend—the primary driver of health expenditures—while maintaining or improving health outcomes.

There are over 50 main recommendations covering all sections in this report, affecting different healthcare stakeholders. There are five primary recommendations specifically targeting Ministers of Health based on those that have the highest impact from a combination of:

1. Low spending level required for implementation.
2. Medium to high improvements in health outcomes.
3. Rapid time from initiation to impact.

Judgement is not made on the feasibility of implementation since this varies substantially by country. Recommendations and underpinning analyses are based on insights from policy interventions and case studies with proven quantified impact from a health outcome and/or cost containment perspective. These evidence-based examples from different countries can inspire health policy leaders to tackle these challenges in a targeted way.

Given the global scope of this report, recommendations are not feasible in a vacuum and the desire or will to make change is not enough. Certain capabilities are necessary for health system leaders to decide whether they can drive change. The following figures summarise five key success factors and their relevance to Ministers based on the ministerial roles of policymaking, leadership, and investment commitment.

However, not all success factors are 100% necessary to drive change. Countries with varied resources can still make an impact. Each recommendation necessitates a different combination of success factors.

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### RECOMMENDATIONS FOCUS IS ON SIX LEVERS THAT CAN IMPROVE MEDICINE USE TO REDUCE OVERALL SPEND AND IMPROVE OR MAINTAIN OUTCOMES

<table>
<thead>
<tr>
<th>Improvements on...</th>
<th>Medicine spend</th>
<th>Nonmedicine spend</th>
<th>Health outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untimely medicine use</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Medication errors</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Mismanaged polypharmacy</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Suboptimal generic use</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Antibiotic misuse/overuse</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

What can ministers do to improve medicine use in these areas?

Improvements may necessitate an increase (shown by the red arrow) or decrease (shown by the green arrow) in medicine spending but manage nonmedicine spending and maintain or improve health outcomes. Nonmedicine spending refers to healthcare costs not associated with the pharmaceutical budget, including the provision of clinical services in primary care and hospital settings. Note that suboptimal generic use does not impact nonmedicine spending or health outcomes since the improvement would be limited to a substitution effect and therefore, reduction in medicine spending only.
## RECOMMENDATIONS

<table>
<thead>
<tr>
<th></th>
<th>RECOMMENDATIONS</th>
<th>LEVERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Support greater role of pharmacists to own medicines management for patients and collaborate with physicians for revision</td>
<td>Nonadherence and Mismanaged polypharmacy</td>
</tr>
<tr>
<td>2</td>
<td>Invest in medical audits targeting elderly patients who are more likely to be taking multiple medicines</td>
<td>Mismanaged polypharmacy</td>
</tr>
<tr>
<td>3</td>
<td>Implement mandatory reporting of antibiotic use by provider</td>
<td>Antibiotic misuse/overuse</td>
</tr>
<tr>
<td>4</td>
<td>Encourage positive attitude and culture towards error reporting by reducing punitive measures against providers who commit errors</td>
<td>Medication errors</td>
</tr>
<tr>
<td>5</td>
<td>Support targeted disease management programmes for prevalent NCDs such as diabetes to ensure timely therapy initiation: not for all patients but for those at highest risk</td>
<td>Untimely medicine use</td>
</tr>
</tbody>
</table>

## FIVE SUCCESS FACTORS THAT CAN BE SUPPORTED BY MINISTERS OF HEALTH FOR IMPLEMENTATION

<table>
<thead>
<tr>
<th>SUCCESS FACTORS</th>
<th>MINISTER’S ROLE</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Policy</strong></td>
<td>Policy</td>
<td>Policies, regulations, or laws that can trigger improvements in medicine use downstream among clinicians, pharmacists, and patients</td>
</tr>
<tr>
<td><strong>Collaboration</strong></td>
<td>Leadership</td>
<td>Multistakeholder engagement among healthcare professionals</td>
</tr>
<tr>
<td><strong>Education and Capacity</strong></td>
<td>Leadership or Policy</td>
<td>Education of either health professionals or patients through training and/or public campaign efforts. Scaled capacity in the health workforce may be required</td>
</tr>
<tr>
<td><strong>Informatics</strong></td>
<td>Financing</td>
<td>Data collection or medicine use monitoring to inform decision making; Includes use of information technology (IT) and non-IT based methods</td>
</tr>
<tr>
<td><strong>Incentives</strong></td>
<td>Financing</td>
<td>Alignment of incentives among healthcare professionals to drive changes in clinical and/or dispensing practice</td>
</tr>
</tbody>
</table>
RECOMMENDATION 1 APPLIES TO BOTH NONADHERENCE AND POLYPHARMACY

SUPPORT GREATER ROLE OF PHARMACISTS TO OWN MEDICINES MANAGEMENT FOR PATIENTS AND COLLABORATE WITH PHYSICIANS FOR REVISION

<table>
<thead>
<tr>
<th>KEY SUCCESS FACTORS</th>
<th>DETAILS</th>
</tr>
</thead>
</table>
| Engage multiple stakeholders, especially pharmacists’ contribution | • Pharmacists are recognised for the value-added role they can play in collaborating with physicians to manage medicines in community and/or ambulatory settings  
• Pharmacists provide regular updated information on medication therapies for physicians |
| Remunerate for additional services | • Add or adjust legislation and/or financing mechanisms to remunerate pharmacists’ time on medication review |
| Collect, track, and analyse data | • Pharmacy dispensing data or insurance claims data are used to monitor medicine use during intake  
• Data informs immediate decision making and interventions based on patient needs and outcomes |
| Easy access to patients (e.g. phone or face-to-face) | • Pharmacists use mobile phones to communicate with physicians and patients about medication regimen changes or reminding  
• Some pharmacists can be based in physicians’ offices to assess medicine use in real-time and provide advice on patients with complex medication regimens |
| Improve communication skills | • Pharmacists receive education to improve their communication skills with patients |
| Reference point | Nonadherence: UK (Medicine utilisation reviews), Germany and Denmark (Pharmacy asthma adherence program)  
Polypharmacy: Health Alliance Plan (US), Home Medicines Review (Australia) |
RECOMMENDATION 2 FOR POLYPHARMACY

INVEST IN MEDICAL AUDITS TARGETING ELDERLY PATIENTS WHO ARE MORE LIKELY TO BE TAKING MULTIPLE MEDICINES

<table>
<thead>
<tr>
<th>KEY SUCCESS FACTORS</th>
<th>DETAILS</th>
<th>RELEVANCE TO OTHER LEVERS</th>
</tr>
</thead>
</table>
| Collect data on elderly patients’ medication regimens | • In countries where e-health systems are in place, all the elderly population are registered with their medication histories; elderly at risk of adverse polypharmacy can be identified  
• Pharmacists' claims data can be used to track elderly patients with multiple medications  
• In countries without an e-health system, elderly people can be registered in a separate system so it is easier to track their medication history | Nonadherence, Medicine abuse, Antibiotic use |
| Mandate regular audits | • Audit and feedback may be a governance or regulatory arrangement, or used in accreditation or organisational assessments | Medication errors, Antibiotic use |
| Remunerate for the service | • Audit and feedback can be linked to economic incentives or to reimbursement schemes, e.g., result-based financing or pay-for-performance schemes | Medication errors, Antibiotic use |

Reference point: UK, Netherlands, Sweden, Belgium, Germany
### RECOMMENDATION 3 FOR ANTIBIOTIC USE

**IMPLEMENT MANDATORY REPORTING OF ANTIBIOTIC USE BY PROVIDER**

<table>
<thead>
<tr>
<th><strong>KEY SUCCESS FACTORS</strong></th>
<th><strong>DETAILS</strong></th>
<th><strong>RELEVANCE TO OTHER LEVERS</strong></th>
</tr>
</thead>
</table>
| Collect data on antibiotic prescribing and dispensing | • Establish a self-reporting system for prescribers to report their antibiotic prescribing rate  
• Track antibiotic dispensing to monitor antibiotic sales; examine instances of sales without prescriptions (if applicable) | Medicine abuse, Generics |
| Summarise and report the data publicly | • Use data to identify specific interventions  
• Institute rewards or penalties according to incentives and disincentives  
• Analyse trends in antibiotic use and resistance; use evidence to update guidelines as appropriate | Medicine abuse, Antibiotic use |
| Institutionalise antibiotic use reporting | • Assess incentives and disincentives for antibiotic use based on reported data  
• Establish national guidelines or regulations to mandate antibiotic use reporting on a hospital and/or individual prescriber basis | Medication errors |
| Invest in human resources to enforce/manage/analyse reporting | • Dedicate resources to monitor and enforce reporting  
• Analyse reports on a monthly/yearly basis to track changes in trend and probe into high prescribing period or region  
• Analyse reports to compare practices with guidelines | Medicine abuse, Antibiotic use |

**Reference point**  
Brazil, South Korea (Antibiotic use published on Health Insurance Review Agency website), Sweden (Strama)
## RECOMMENDATION 4 FOR MEDICATION ERRORS

### ENCOURAGE POSITIVE ATTITUDE AND CULTURE TOWARDS ERROR REPORTING

<table>
<thead>
<tr>
<th>KEY SUCCESS FACTORS</th>
<th>DETAILS</th>
<th>RELEVANCE TO OTHER LEVERS</th>
</tr>
</thead>
</table>
| Establish policies that encourage disclosure of errors   | • Adopt a formal policy at the hospital level of total disclosure of errors to patients, accompanied with changes of corresponding liability laws  
• Establish policies in hospitals to actively encourage error disclosure by health professionals | Antibiotic use             |
| Engage all healthcare workers                            | • Encourage all health workers (physicians, pharmacists, nurses, and other health works) to participate in medication error reporting | Antibiotic use             |
| Provide a system for error reporting                     | • Build up an error reporting system at hospital level and/or national level  
• Promote the use of the system to healthcare workers and increase their awareness of the available channels of error reporting  
• Analyse and update regularly the trends and reasons for medication errors | Antibiotic use             |
| Educate health professionals on how to report errors and how to reduce errors | • Train health professionals on how to use and document in existing reporting systems  
• Educate healthcare workers on how to reduce errors with the updated information and trends in medication errors | Antibiotic use             |

Reference point: Oman, Sweden, Brazil
### RECOMMENDATION 5 FOR TIMELY MEDICINE USE

#### SUPPORT TARGETED DISEASE MANAGEMENT PROGRAMMES FOR PREVALENT NONCOMMUNICABLE DISEASES IN PATIENTS AT HIGHEST RISK

<table>
<thead>
<tr>
<th>KEY SUCCESS FACTORS</th>
<th>DETAILS</th>
<th>RELEVANCE TO OTHER LEVERS</th>
</tr>
</thead>
</table>
| Set up a data tracking system | • Establish a web-based database to register and track patients’ information and identify those at highest risk, and link to stakeholders’ endpoints at the same time  
• Issue reminders to providers (regarding patient’s progress) and patients (regarding overdue tests and appointments)  
• Prompt automatic treatment suggestions when certain physiological indicators are elevated to a threshold | Polypharmacy, Nonadherence, Medicine abuse |
| Engage multiple stakeholders | • Encourage participation by physicians, pharmacists, and nurses in the disease management programme  
• Obtain support from community hospitals, secondary care hospitals, pharmacies, and laboratories | Medication errors |
| Invest in remuneration and infrastructure | • Provide remuneration for health professionals’ additional time, assured by policies or legislations  
• Invest in the infrastructure (e.g., IT system, fast-track insulin clinics) to operate the programme | Polypharmacy, Nonadherence |
| Educate on communication skills and IT use | • Educate all stakeholders on the use of the IT functions  
• Increase training for health professionals on patient counselling skills in the inpatient setting | Polypharmacy, Nonadherence |

**Reference point**
US (The Southern California Permanente Medical Group on diabetes care), German diabetes management programme, Canada British Columbia PharmaNet
IV. Medicine use revisited: Six primary levers of opportunity

All countries can improve use of medicines across six levers to reduce avoidable costs.
All countries can improve use of medicines to reduce avoidable costs.

These figures are estimates derived from a global modelling analysis of the avoidable cost opportunity based on best available data from different countries.

The purpose of this analysis is to trigger a meaningful discussion not on the exact figures but rather on how to assess the impact of more responsible use of medicines.

Sources: IMS Institute for Healthcare Informatics, 2012; IMS MIDAS, 2009 and 2011; World Bank 2009; WHO 2009; USD in 2011. See Methodology section for details on global calculations that include 186 countries.
IV. MEDICINE USE REVISITED: SIX PRIMARY LEVERS OF OPPORTUNITY

All countries can improve the use of medicines. The research in this report identified and quantified the estimated impact of six primary levers of suboptimal medicine use. The summary of this analysis is presented in Figure 1. Regardless of the country income or current medicine access, all health system leaders can move the needle on nonadherence, untimely medicine use, antibiotic misuse and overuse, medication errors, suboptimal generic use, and mismanaged polypharmacy.

Why the country variation?

Figure 1 demonstrates the opportunity and potential focus for Ministers of Health and health system leaders. The analysis is deliberately not meant to support a ranking of countries or be taken out of this context. It is constructed through careful estimations given best available data both in terms of quality and quantity. As such, it provides guidance rather than a prescriptive direction.

The backbone of these estimations and their variation are five main factors that were identified from the findings of this research:

1. Health system infrastructure: Strong infrastructure (e.g., human resources and capital) can be a positive or negative factor for optimal medicine use. The direction of impact depends on the quantity (e.g., number of physicians, pharmacists) and quality (e.g., processes and incentive alignment) of infrastructure. The latter is not measured due to lack of data. Greater infrastructure in terms of quantity is likely to increase medication error risk, mismanaged polypharmacy, and antibiotic misuse and/or overuse purely because there is greater room for error. On the other hand, more infrastructure may also mean that patients are treated in a timely manner and can be better supported to appropriately take their medicines.

2. Noncommunicable disease (NCD) risk factors: All countries face an increasing NCD burden. This burden is exacerbated by a variety of risk factors that, if not managed, result in severe health system and societal burdens. Excess alcohol consumption, smoking and tobacco intake, and obesity increase the risk of chronic illnesses such as coronary heart disease, hypertension, and diabetes, thereby increasing the need for medicines. Paradoxically, greater medicine need combined with the availability of medicines is likely to contribute to suboptimal medicine use.

3. Affordability: Much like infrastructure, affordability can be a positive or negative factor for optimal medicine use. It may have a positive impact on challenges such as suboptimal medicine use since countries with higher affordability will be more aggressive in attempts to increase access to low-cost medicines. Affordability also reduces untimely medicine use since patients are less likely to reject care on the basis of income. On the other hand, greater access to medicines carries higher risk of error with medication errors and mismanaged polypharmacy.

4. Elderly: An ageing population is accompanied by increasing comorbidities (both chronic and acute), and with them comes a need for more medicines. Countries with higher elderly populations also have higher medicine use: this relationship is likely more correlative than causative. Mismanaged polypharmacy is the greatest risk with an increasing elderly population.

5. Medicine intensity: Medicine intensity refers to the general volume of medicines in the system, including the number of new chemical entities available and antibiotic use. It appears to be positively correlated with some suboptimal use levers, and negatively correlated with others. Specifically, with more medicines available there is a greater likelihood of error, polypharmacy, and abuse. Conversely, increased medicine intensity may improve timely use as newer agents may be more effective and replace the previous standard of care. However, apart from gains in timely medicine use, this factor increases the risk for negative impact on all other levers. Antibiotic use is assessed as having an independent effect on antibiotic misuse/overuse only.
The combination of these factors and how they differ across countries explains the variation. A country like the UK has a relatively strong health system infrastructure, high affordability, a high level of medicine intensity, and a greater proportion of elderly. Therefore it has greater likelihood of medicine use-related challenges such as medication errors, mismanaged polypharmacy, and antibiotic misuse/overuse. However, the UK has less to gain from generic use, as policies have been in place historically to regulate and support safe use of low-cost medicines and the country is relatively better able to support timely medicine use.

Countries such as Bangladesh, Ghana, and Vietnam have a different set of challenges more related to untimely medicine use and suboptimal generic use. The infrastructure is not in place to support responsible medicine use. Since medicines have limited accessibility, avoidable costs are primarily driven by late or nonexistent interventions to diagnose, screen, and monitor patients. This also explains why antibiotic misuse and/or overuse varies for countries and why medication errors are limited. Challenges related to mismanaged polypharmacy are rare given the relatively low elderly population in such countries. Additionally, NCD risks such as obesity are also not as prevalent in these countries. Suboptimal generic use is a challenge in countries like these given the relatively weak regulatory capacity to set up effective pharmaceutical policies and competing priorities. There are greater challenges beyond the scope of medicine use. Issues related to medicine access and economic development are paramount.

Assessing an individual country’s health system and medicine use elements is necessary to accurately quantify the level of country variation and therefore the real magnitude of opportunity from the levers for improved medicine use.

Further details on these estimates may be found in the Methodology section of this report.
IV. Medicine use revisited: Six primary levers of opportunity

1. PATIENT USAGE

Increase adherence

Nonadherence contributes 57% of the world’s total avoidable cost due to suboptimal medicine use.
1. PATIENT USAGE: INCREASE ADHERENCE

Nonadherence contributes 57% of the world’s total avoidable cost due to suboptimal medicine use.

A total of 4.6% of global total health expenditure (THE), or 269Bn USD worldwide, can be avoided from adherence to medicines.

Country variation is driven by a number of factors discussed in this section. The higher bars denote countries with more medicines in the system. This is offset by healthcare infrastructure; greater infrastructure implies a stronger health system ability to minimize the number of nonadherent patients.

Figure 2 below provides a snapshot summary of relative avoidable costs out of THE. Data and respected ranges were estimated based on a combination of estimated and real values as well as data reliability. Where there are only two points, the point estimate is the minimum. Global average values are weighted by country total health expenditure.

Ministerial relevance and recommendations

- Addressing this challenge requires a targeted approach; risk-stratifying patients is beneficial to avoiding costs and also incurring savings, as well as improving health outcomes.
- Nonadherence does not necessarily save costs but some patients may experience improved health outcomes when interventions work.

Source: IMS MIDAS, 2009 and 2011; World Bank 2009; WHO 2009; USD in 2011; Please see methodology section for details on global calculations which include 186 countries
1. INCREASE ADHERENCE

RECOMMENDATIONS (1/2): ADDRESS NONADHERENCE THROUGH RISK STRATIFICATION, TARGETED EDUCATION, AND INDUSTRY COLLABORATION

<table>
<thead>
<tr>
<th>POTENTIAL MOH INTERVENTIONS</th>
<th>REFERENCE POINT</th>
<th>SPEND</th>
<th>HEALTH OUTCOME</th>
<th>TIME SCALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collect (or encourage collection of) data that supports and encourages risk stratification of patients for nonadherence risk factors to subsequently target interventions at point of prescription and then medication intake</td>
<td>IMS Health (Persistence data)</td>
<td>Low cost</td>
<td>Medium</td>
<td>0-2 years</td>
</tr>
<tr>
<td>Train and educate health professionals on adherence issues in the work place and academic institutions</td>
<td>UK (Incorporated into pharmacists’ education curriculum at institutes)</td>
<td>Low cost</td>
<td>Medium</td>
<td>3-5 years</td>
</tr>
<tr>
<td>Establish community-based programme for peer-to-peer counselling and social support to encourage medicine use for targeted patients</td>
<td>Sub-Saharan Africa (ARV) Indonesia (CBIA education on diabetes) UK (Macmillan Cancer Support)</td>
<td>Moderate cost</td>
<td>Medium</td>
<td>0-2 years</td>
</tr>
<tr>
<td>Collaborate with industry to develop adherence-supportive packaging and commercial adherence programme</td>
<td>Merck-Cigna (US) Pay for Outcome programme for diabetes medicines</td>
<td>Low cost</td>
<td>Medium</td>
<td>2-3 years</td>
</tr>
</tbody>
</table>

Basis for recommendations: Interventions and policy options

CHALLENGES WITH INTERVENTION ANALYSIS RELEVANT FOR A MINISTERIAL AUDIENCE

A significant amount of research has been conducted in recent decades to explore effective interventions on nonadherence (Haynes et al. 2002; Lin et al. 2012; Lin and Ciechanowski 2008; Van Dulmen et al. 2008). Most of these were attempted on a limited scale in certain disease areas or classes of medicines but few interventions have been seen on a national level. There might be several possibilities for why national-level intervention implementation has been scarce. One possibility could be the financial resources required for adherence interventions. The second reason might be extra human resources needed to manage medicine intake. Another challenge lies in the complex nature of nonadherence. Since nonadherence is attributed to multiple risk factors, addressing one risk factor does not always solve the whole issue. In other words, the return on investment for a specific intervention may be unpredictable and impossible to guarantee.

However, specific interventions that target specific diseases and stakeholders have been carried out in some countries, suggesting that customised interventions for high-risk patients with certain characteristics can work. For example, in 2006 the US initiated nationwide efforts in pharmacist-led medication therapy management (MTM) services to address medicine-related issues with a focus on patient nonadherence, and strengthening the use of pharmacists’ expertise. The Brazilian Ministry of Health covers antiretroviral (ARV) treatment for all
HIV-positive patients in the country and supports this effort with a multiprofessional medical team at points of service to ensure adherence to medication. Patients receive Specialised Care Services (SAE), a patient-centric programme providing educational activities to support patient adherence to HIV medication. These efforts demonstrate the potential for nationwide programmes that target specific patients.

There are four main areas of intervention for Ministers of Health to consider:

1. Adopt cross-disease learnings.
2. Apply a shared decision-making and patient-centric approach.
3. Support data collection efforts that enable healthcare professionals to target interventions where and when they will change patient behaviour.
4. Strengthen the roles of healthcare professionals, particularly pharmacists, to support targeted patient adherence interventions.

These points and the related evidence are discussed in turn.

### IV. Medicine Use Revisited: Six Primary Levers

<table>
<thead>
<tr>
<th>Potential MOH Interventions</th>
<th>Reference Point</th>
<th>Spend</th>
<th>Health Outcome</th>
<th>Time Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convene healthcare professionals and industry experts to identify consistent indicators for measuring adherence and ensuring appropriate data collection to assess adherence for different diseases</td>
<td>International organisation collaboration (Management Sciences for Health, International Society for Pharmacoeconomics and Outcomes (ISPOR))</td>
<td>Low cost</td>
<td>Low</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Learn best practices from ARV medicines track record for other disease management initiatives: engaging patients as peer experts, low-burden reminder system (e.g., SMS use), regimen simplification</td>
<td>Kenya, Uganda, Brazil</td>
<td>Moderate cost</td>
<td>Medium</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Support and encourage pharmacist- or physician-led medication therapy management programme to monitor patients and modify medication regimens</td>
<td>Germany and Denmark (Asthma adherence programmes) UK (MUR)</td>
<td>Moderate cost</td>
<td>High</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Use data and capabilities informatics (MEMS, e-prescribing system, text messages or e-mails) to identify patients who adhere and do not and to prompt adhering behaviour</td>
<td>Netherlands (Internet Patient Portal Mijn Gezondheid.net), US Walgreens options for electronic reminding</td>
<td>Low cost</td>
<td>High</td>
<td>3-5 years</td>
</tr>
</tbody>
</table>
1. ADOPT CROSS-DISEASE LEARNINGS

Although nonadherence rates differ by disease, interventions for one disease can provide useful insights for others. Examples of various diseases are provided throughout this section to demonstrate the cross-learning opportunity. Examples from ARV treatment for HIV-positive patients are bountiful due to decades of research that has been done in both developed and developing countries; intervention programmes that have been implemented in resource-poor settings at low cost; and because HIV has common features with other chronic diseases in terms of nonadherence risk factors.

Lessons also can be drawn from cardiovascular (CV)-related diseases. Given the large expenditures on disease and avoidable costs from nonadherence in CV-related disease areas such as diabetes, hypertension, and hypercholesterolemia, it is not surprising that high-income country adherence research has focused on studies involving CV agents such as antihypertensives and statins. In fact, CV medicines adherence has wide applicability to other treatment areas that share some or all of the risk factors for nonadherence: chronic treatment often involving multiple pills, asymptomatic features, adverse effects, and a range of patient-related factors (e.g., age, income, etc.).

Besides CV and HIV, research also draws on interventions related to other diseases such as asthma and depression, a major comorbidity with chronic diseases. Depression is found to be associated with nonadherence among patients with diabetes (Gonzalez et al. 2008; Lin et al. 2004; Linn et al. 2011), hypertension (Hashmi et al. 2007), and HIV (Gonzalez et al. 2011). Interventions for patients with mental health diseases should also differ from other adherence interventions as the reason for the nonadherence is related to the illness itself. A main reason for the mentally ill to not take medicines is that they do not believe they have an illness (anosognosia) (Kessler et al. 2001; Mental Illness Policy Organization 2011).

2. APPLY A SHARED DECISION-MAKING AND PATIENT-CENTRIC APPROACH

Regardless of terminology and methods, the patient-centric approach underlines all adherence interventions. Studies exploring patient-centred care found that engaging patients as decision-makers is associated with improved adherence (Parchman et al. 2010; Robinson et al. 2008; Schneider et al. 2004; Wilson et al. 2010). In the ‘shared decision-making’ model, doctors provide patients with disease knowledge (condition, progression, self-management skills, etc.), or they already demonstrate expertise about their health conditions through self-education and can therefore be considered ‘experts.’ Instead of passively accepting doctors’ recommendations, patients make their own decisions on treatment. This shared decision making has been shown to be effective in improving adherence in type 2 diabetes control (Parchman et al. 2010), asthma treatment, and HIV (Schneider et al. 2004; Wilson et al. 2010). The UK Medicine Adherence Guideline published in 2009 by National Collaborating Centre for Primary Care (NCCPC) at the National Institute for Health and Clinical Excellence (NICE) included ‘Shared decision making’ as a recommended strategy to improve adherence (National Institute for Health and Clinical Excellence 2009; Wilson et al. 2010).

This is also an approach healthcare professionals can actively take if they are mandated to do so. Healthcare professionals cannot control a number of risk factors for nonadherence. Patient-centric and tailor-made interventions are ones that they can control, influence and should, therefore, focus on (Van Dijk 2012; Wilson et al. 2010).

Engaging patients as experts has proven to work for medication adherence, particularly for chronic disease patients. Historically, patients have been underutilised healthcare resources and can provide peer support to other patients with accumulated expertise and emotional sympathy. This has been shown as an effective strategy to improve adherence to ARV treatment in resource-poor settings (Arem et al. 2011; Angego et al. 2009). The Rakai Health Sciences ARV Therapy Programme in Uganda engages trained HIV-positive peer educators to serve as role models to other patients (Chang et al. 2008). These trained peers provide emotional support and personalised counselling to patients.
Table 1 provides examples of evidence that this approach can improve adherence and therefore, outcomes.

Diabetes is a particularly relevant disease area where patient empowerment is critical given the high level of self-management and care required. Healthcare professionals overseeing patients with diabetes are increasingly recognising the ‘patient empowerment’ approach whereby healthcare professionals collaborate with the patient to inform and support them in making the best possible diabetes self-management decisions and ensure patient adherence (Anderson and Funnell 2005; Hurwitz and Sheikh 2011; Kharrazi 2009).

Improving patient self-management skills: Patients’ development of self-management skills has a direct positive effect on improving adherence, though these interventions are not well documented or tracked. Anecdotal evidence from focus groups conducted in the Netherlands by the Netherlands Institute for Health Services Research (NIVEL) suggest that patients actively help with adherence through simple tactics, such as placing their pills next to coffee makers or other habit-related actions that trigger medicine intake (Van Dijk 2012). Increasingly, technology such as smartphone applications helps patients with self-management as they can use applications to send data electronically to clinics and obtain advice rapidly on a range of diseases. Because this is relatively new modality (~since 2008 with the boom of smartphones) outcomes assessments are not yet available. However, Andrew Lansley, the UK’s Health Secretary, acknowledged the potential contribution smartphones may make in this field. He recently compiled a list of healthcare applications that he is urging general practitioners (GPs) to recommend to their patients (Smyth 2012). Such approaches are rampant with concerns about consistency and information quality but merit continuing research. Because most recent and historic research has focused on how to improve what does not work rather than highlight what does work consistently, these interventions are underreported and underinvestigated.

3. SUPPORT DATA COLLECTION EFFORTS WHICH ENABLE HEALTHCARE PROFESSIONALS TO TARGET INTERVENTIONS THAT WILL CHANGE PATIENT BEHAVIOUR

A two-step approach to understanding adherence interventions is proposed. This approach is grounded on the fundamental need to collect data and information about
patient behaviour to develop a targeted approach at both the point of prescription and dispensing during medication intake. At the point of prescription and dispensing, data can inform nonadherence risk factors early and reduce primary nonadherence (refers to not filling initial prescription). During medication intake, data can inform intake adherence defined as the quality of medicine intake (dose, frequency, regularity) and persistence as the duration of medication intake (de Decker et al. 2011).

In general, the most effective interventions target patients at higher risk and tailor to their needs, resulting in a more profound outcome from health and cost perspectives. This philosophy predominantly stems from business marketing expertise that aims to change consumer behaviour. However, as a case-in-point, Ipsos Healthcare of American marketing firm Ipsos, demonstrated exactly these principles in research they have done to define attitudinal and behavioural drivers of persistence. The results of their work segmented patients

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### TABLE 2: RISK-STRATIFYING PATIENTS AND TARGETED INTERVENTIONS IMPROVED ADHERENCE LEVELS AND HEALTH OUTCOMES

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>RISK GROUP</th>
<th>INTERVENTIONS</th>
<th>OUTCOMES - ADHERENCE LEVEL</th>
<th>OUTCOMES - HEALTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al. 1997</td>
<td>Hypertensive patients ≥60 years old whose systolic blood pressure (SBP) is ≥160 mm Hg or whose diastolic blood pressure (DBP) is ≥90 mm Hg</td>
<td>Regular medical care plus the telephone-linked computer system (TLC), an interactive telecommunications system that converses with patients in their homes, using computer-controlled speech.</td>
<td>Mean antihypertensive medication adherence improved 17.7% for telephone system users and 11.7% for controls</td>
<td>Mean DBP decreased 5.2 mm Hg in users compared to 0.8 mm Hg in controls. Among nonadherent subjects, mean DBP decreased 6.0 mm Hg for telephone users, but increased 2.8 mm Hg for controls</td>
</tr>
<tr>
<td>Friedman et al. 1996</td>
<td>Elderly men and women patients (&gt;65 years old) taking 4 or more chronic medications daily</td>
<td>A 6-month intervention phase, including standardised medication education, regular follow-up by pharmacists, and medications dispensed in time-specific packs</td>
<td>After 6 months of intervention, medication adherence increased from baseline 61.2% to 96.9%.</td>
<td>Significant improvements in SBP (133.2 to 129.9 mm Hg) and LDL-C (91.7 to 86.8 mg/dL)</td>
</tr>
<tr>
<td>Lee et al. 2006</td>
<td>Hyperlipidemia and coronary artery disease patients who are aged ≤65 years old at high risk of future cardiac events</td>
<td>Simplified niacin dosing regimens: from 4 times daily (regular) regimen to 2 times daily dosage (controlled)</td>
<td>95% with controlled-release niacin vs. 85% with regular niacin</td>
<td>The target of LDL-C (Low-density-lipoprotein cholesterol)≤100 mg/dL was achieved at 8 months by 83% of these patients with controlled-release niacin, and by 52% with regular niacin</td>
</tr>
</tbody>
</table>
by behaviour types and concluded that targeted interventions are the best return on investment (IPSO 2006). At the point of prescription, an assessment of patients’ nonadherence risk factors helps identify patients at higher risk of nonadherence. This can then inform a targeted monitoring or reinforcement plan during medication intake to minimise secondary nonadherence (rates of medication use).

Because patients’ compliance tends to decrease over time, connecting with them as soon as they get their prescription is crucial. Physician interaction is critical in this initial process. Evidence from adherence to lipid-lowering therapy shows physician interaction early in treatment is key to downstream adherence (Benner et al. 2004). Pharmacist engagement is also highly impactful since they see patients more than any other healthcare professional in this phase (Center for Health Transformation 2010). In summary, spotting the problem at medication initiation and subsequently acting on it is more likely to increase adherence and reduce long-term costs than initiating intensive interventions and correcting nonadherence down the line. Both prescribers and pharmacists can play a role in this process.

Data collection on patient characteristics is a powerful tool to identify nonadherence risk factors. Once these are identified for a population, they can be used as a checklist for healthcare professionals to better understand patient needs (and risks). Targeted interventions can then be planned to maximise adherence.

Targeted interventions for patients at higher risk were associated with improved adherence levels and health outcomes. Table 2 on the previous page provides nonexhaustive examples of evidence.

Drug manufacturers have tools to help segment patients by risk levels. For example, Merck developed a proximal psychometric test of three simple questions for doctors to stratify patients according to their risk levels of nonadherence and identify patients at higher risk (McHorney 2009). Another commercial segmentation focus is a targeting model that stores patients’ historical adherence data, maps out patients’ geographic or demographic characteristics, and predicts behaviour tendency for new patients.

A more advanced health IT system could enable segmentation by comparing data from e-prescribing and pharmacy refill information. For example, IMS Health analyses persistence using claims data from the US and longitudinal patient data records from Germany to identify characteristics of patients who do not adhere to medicines and provides insights on the rationale.
4. STRENGTHEN THE ROLES OF HEALTHCARE PROFESSIONALS, PARTICULARLY PHARMACISTS, TO SUPPORT TARGETED PATIENT ADHERENCE INTERVENTIONS DURING MEDICATION INTAKE

Effective interventions to improve adherence during medication intake requires a multifactorial approach. Healthcare professionals, industry, patients, and community are all active stakeholders that can play a role in achieving better results.

However, interventions by healthcare professionals will also be effective if they are targeted, and consistent. Data collection can help. The same data used to identify patient nonadherence risk factors can also be used to track whether specific adherence interventions work. For example, a recent study by IMS Health researchers used IMS data to find that certain interventions for statin/antihypertensive medications such as reminders, educational materials, and case management programmes led by pharmacists or nurses can be cost-effective as a first step to improve adherence (Chapman et al. 2010). Figure 3 provides a summary of this.

This analysis demonstrates a critical realisation, which is that improving adherence will require an investment. Although improving adherence drives up the overall medicine costs, it can provide economic return from reduced overall healthcare costs (Roebuck et al. 2011; Sokol et al. 2005). Even accounting for the intervention cost, research on a pharmacy-based, in-person management programme showed the expenses could be offset by economic benefits: a return on investment of approximately 3 USD for every 1 USD spent (Brennan et al. 2012). In this review, the greatest relative improvement was for an intensive management programme of monthly pharmacist monitoring during follow-up.

FIGURE 3: SPECIFIC INTERVENTIONS CAN BE COST EFFECTIVE WHEN TARGETING STATINS AND ANTIHYPERTENSIVE MEDICINE ADHERENCE

![Graph showing specific interventions can be cost effective when targeting statins and antihypertensive medicine adherence.](image)

*Relative improvement = risk of the event occurring in the intervention group divided by the risk of the event occurring in the control group over 6 months*
Healthcare professionals such as nurses and pharmacists can do more to intervene when it comes to nonadherence. Figure 4 above summarises the different interventions each stakeholder type can act upon individually. The following discussion goes into more detail on each stakeholder.

As Ministers of Health consider strengthening the roles of healthcare professionals beyond just dispensing and transcribing (by pharmacists and nurses), they can consider **task shifting** as a concept underlying these recommendations. Task shifting is a strategy to delegate tasks performed by physicians to staff with different (or lower level) qualifications. This concept has traditionally been considered in the context of insufficient human resources for health in low-resource settings, primarily in administering and monitoring patients on HIV treatment. However, learnings from this research may be relevant for all countries in terms of identifying ways to shift tasks and offer better medicine management, particularly in the context of chronic diseases. In particular, pharmacists can be leveraged to apply the risk-stratification approach during dispensing at the start of medicine intake and during the medication intake process as well. From one HIV treatment program in Lusikisiki, South Africa, the role of pharmacists and their assistants in checking patient adherence and identifying patients who default on treatment played a part in the 17% reduction seen in the number of patients lost from treatment follow-up programs (Bedelu et al. 2007; Zachariah et al. 2009). Supporting and paying staff for new roles and the integration of new members in health teams must all be considered (Callaghan et al. 2010; Fulton et al. 2011).

**Strengthening the role of pharmacists:** Clinicians are often regarded as the primary educators on medication because they make prescribing decisions and patients trust their instructions. Recent findings reveal the roles of pharmacists and nurses have been underutilised in addressing nonadherence in community care. As frontline healthcare providers, pharmacists are most accessible in the community but currently spend 55% to 57% of their time dispensing, less than 20% providing consultation, and 8% in medicine therapy management (Gerald 2010). Their

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**Figure 4: Other Unique Interventions Related to Each Stakeholder**

<table>
<thead>
<tr>
<th>CLINICIANS</th>
<th>NURSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Monitor medication over time</td>
<td>- Monitor medication over time</td>
</tr>
<tr>
<td>- Simplify or modify regimens</td>
<td>- Simplify or modify regimens</td>
</tr>
<tr>
<td>- Tailored regimens</td>
<td>- Tailored regimens</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PHARMACISTS</th>
<th>COMMUNITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Refill reminding</td>
<td>- Supervise patients</td>
</tr>
<tr>
<td>- Compliance aids in dispensing, e.g. multicompart box</td>
<td>- Provide social and emotional support</td>
</tr>
<tr>
<td>- Medication therapy management (MTM) and monitoring during medicine intake</td>
<td></td>
</tr>
</tbody>
</table>

Sources: IMS Institute for Healthcare Informatics, 2012.
role should shift from purely dispensing to that of a more integrated health service provider who utilises knowledge and expertise in counselling and medication management. Pharmacists can contribute more given their frequent interactions with patients and their knowledge of medicines.

Health care systems are becoming increasingly aware of pharmacist expertise in managing patients’ medications. In the UK, national guidelines and policies provide a greater scope for pharmacists to support patient adherence (Clifford et al. 2010). Interventions that appropriately leverage pharmacists for adherence interventions include:

a. Reinforcing pharmacist education in academic settings: In the UK, most pharmacist education institutes incorporate medication adherence into the curriculum in undergraduate and postgraduate programmes (Clifford et al. 2010).

b. Refill reminders (by Short Messaging Service (SMS), telephone, or mail): Refills reminders have been executed by pharmacies at a chosen number of days before the patients’ dispensing date is due. A great deal of evidence has been provided for the effectiveness of this programme (Ascione et al. 1985; Rosalind et al. 2010).

c. Compliance aids/dose dispensing: Automated technologies are used in pharmacies to package multimedcine regimens into a single bag with the exact types and number of medicines to be taken in the morning, midday and night (e.g. multicompartiment aids). A pharmacy care program incorporating such blister packaging among elderly patients with coronary risk factors led to increased medication adherence and clinically meaningful reductions in blood pressure. Discontinuation of the programme was associated with decreased medication adherence (Lee et al. 2006).

d. Medication therapy management (MTM): The core elements of an MTM programme includes development of patient medication records (PMR), implementation of a medication-related action plan (MAP) review of medicine use, referral or collaboration with nurses or physicians, and follow-up.

i. The Asheville Project in the US showed that utilising pharmacists’ expertise delivered positive health outcomes and reduced health costs. The Blue Cross/Blue Shield study reported that the return of MTM service is 12 times more than investment (National Association of Chain Drug Stores 2011).

ii. In the UK, Medicine Use Reviews (MUR) is an advanced free service offered for patients to discuss their medications with qualified community pharmacies, which could indirectly help improve patients’ adherence. The UK compensates pharmacists for the extra work that they do. Other systems contemplating similar strategies would need to consider the change in pharmacist workload and implications for compensation.

Recent legislation in France has recognised the greater role of the pharmacist by introducing a capitation fee pharmacists receive per patient for adherence-related services they provide (Le Pen 2012).

Figure 5 on the following page, summarises the evidence in terms of improved adherence from similar combinations of interventions pharmacists can lead.

There is a need to systematically track the additional benefits of pharmaceutical care. The Council of Europe EDQM (European Directorate for the Quality of Medicines and HealthCare) Committee of Experts has made efforts towards this goal by developing indicators as a method to stimulate and evaluate the outcomes of pharmacist-led pharmaceutical care programmes. Although in the development stages, their indicators monitor the number of pharmaceutical care interventions delivered, the number of patients counselled, the number of adverse drug event reports, and the number of feedback responses from patients or caregivers regarding their satisfaction compared against a standardised denominator.
Strengthening the role of nurses: Nurses collaborate with other healthcare providers to ensure medications are prescribed and delivered to patients. Moreover, nurses educate patients on how to take medication before hospital discharge and assess patients’ understanding of medication and ability to adhere to the care plan.

The Heart Failure Society of America consensus guidelines for patients with chronic heart failure stated that nurses were the primary providers of education on heart failure (Adams et al. 2006). Patients reported higher satisfaction on nurse-led care compared to enhanced primary care (defined as physicians receiving recommendations based on national guidelines) because nurses tend to provide longer consultations and more information (Becker et al. 1998). A recent review found that hospital discharge instruction about medications from both nurses and pharmacists are influential in encouraging patients to stay on their medications (Sandberg 2010). When the treatment for chronic diseases takes place at home and in community settings, community nurses can provide a link between patients and clinical services via home visits, phone calls, or reminders.

Strengthening the role of physicians: The major responsibility of physicians is to assess patients’ conditions, prescribe the right medicines, and educate patients at the point of care. In addition, physicians can help with patient adherence by:

a. Monitoring patients over time: A study among patients routinely taking inhaled corticosteroids found the adherence rate was significantly higher in the group followed by physicians using e-prescribing to track medication refills and to monitor medication use (Lewis 2010). Additionally, patients who see their doctors more often tend to be more adherent, but this is also at a fairly high cost (Van Dijk 2012).

### IV. MEDICINE USE REVISITED: SIX PRIMARY LEVERS

<table>
<thead>
<tr>
<th>INTERVENTIONS IN PRIMARY CARE SETTINGS</th>
<th>IMPROVEMENT ON ADHERENCE, % CHANGE</th>
<th>REQUIRED INVESTMENT LEVEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic heart failure: Education, counselling, reminding, and follow-ups</td>
<td>11%</td>
<td>Low</td>
</tr>
<tr>
<td>COPD: Education, counselling, reminding, and record keeping</td>
<td>12%</td>
<td>Medium</td>
</tr>
<tr>
<td>General: Counselling and education (accompanied with reminding messages)</td>
<td>13%</td>
<td>Medium</td>
</tr>
<tr>
<td>General: Medication therapy management</td>
<td>20%</td>
<td>High</td>
</tr>
<tr>
<td>General: Education, dosing, dispensing, and follow-ups</td>
<td>30%</td>
<td>High</td>
</tr>
</tbody>
</table>

Examples from studies in primarily high-income countries that consistently resulted in improved outcomes

b. Modifying regimens or changing doses: A study of patients with high blood pressure in ambulatory settings indicated that simplifying dosing regimens appeared to increase adherence to blood pressure lowering medication (Schroeder et al. 2004). Similar conclusions were drawn from an asthma regimen simplification study. The type of device may also affect patients’ adherence to inhaled corticosteroid treatment (Roy et al. 2011). Therefore, doctors should consider modifying regimens and device suitability when providing corticosteroid treatment. Tailored regimens have better adherence results: tailored ARV regimens in the first 16 weeks were associated with greater self-reported adherence to treatment. Simplifying or tailoring regimens with a lighter pill burden generally can achieve better adherence in ARV treatment (Jordan 2002).

The pharmaceutical industry is playing an increased role in addressing medication nonadherence through specific interventions, yet the evidence that this is beneficial is fragmented and weak from an outcomes perspective. One example with concrete outcomes is that of Merck’s cost-sharing deal with US payer Cigna to link the cost of its diabetes medicines with adherence performance. Greater discounts are provided if patients demonstrate controlled blood sugar, additionally supporting Cigna to offer lower copayments to patients. Merck reimburses Cigna even if patients’ outcomes improve using other medicines. Cigna invested in patient adherence programmes, including phone follow-up to check on nonadherence (Capgemini 2011).

Results are compelling:

- Blood sugar levels improved on average by over 5%.
- Emergency department (ED) and hospital visits were reduced by 50% for those reaching blood sugar goals.
- Diabetes-related costs were reduced by 24%.
- Adherence improved for all medicines and was 87% for Merck’s two drugs.

Ministers of Health can learn from examples like this to encourage cost sharing with manufacturers for specific medicines.

Companies also invest in innovative ways to improve packaging: Pfizer’s Z-pack emphasised the importance of adherence in written instructions on packaging. Calendar Blister Packaging or CBP (in which each tablet’s blister is labelled with a date to provide visual assistance for patients to take medication) showed modest improvement on medication persistence and highlights the future trend of adherent packaging (Zedlar et al. 2011).

Pharmaceutical and medical device companies have increasingly developed applications for smart phones and other devices to improve medicine adherence and management more generally. For example, SIMpill developed pillboxes to send messages to clinicians through wireless technologies if the patient opens the box at the designated time. If not, clinicians follow up with patients by phone (Barclay 2009; Jordan 2002). This resulted in a 94% compliance rate in a tuberculosis trial in South Africa.

The consultancy PricewaterhouseCoopers estimates that treatment services, especially for chronic diseases in Europe, will be primarily delivered through smart phone applications by 2017 (PricewaterhouseCoopers 2012). Currently, such developments specifically focused on adherence are fragmented and nascent; many companies create their own devices for their medicines and there is little evidence and/or consistency on what has actually been proven to work.

Education targeting health professionals and patients: Healthcare providers should receive training on the importance of adherence and skills on how to encourage adherence among patients. As e-health and Information Technology (IT)-based interventions are increasingly used, training should also help healthcare providers leverage technology resources. For example, this can be done by encouraging a positive attitude towards using such tools for risk stratification and patient segmentation.
Community and social network: Family, friends, peer groups, and community workers provide supervision and emotional support for patients. A high level of adherence to ARV therapy was observed to be closely associated with supportive social relationships in sub-Saharan Africa (Alcorn 2009). The mechanism behind this is likely to be an improved state of mind that increases the patient’s confidence in taking the medication (Gonzalez et al. 2008).

Community-Based Intervention Association (CBIA) educational programme among diabetic patients in Indonesia reported better knowledge and a 13% increase (30% vs. 16.7% at baseline) in adherence rate as a result of community-based support (Hartayu et al. 2000). This approach trains pharmacy students to develop educational materials and hold regular small group discussions among patients and their family members to discuss medicine use challenges. CBIA is a potential model of public education for other chronic health issues (Hartayu et al. 2000). Disease-related charities such as Macmillan Cancer Support in the UK provide medical and financial support to cancer patients for medicine adherence (Macmillan Cancer Support 2012).

E-health and IT to monitor and improve adherence: The greater health system push towards using health informatics and related IT systems also improves patient adherence. Technology-based interventions can be targeted and timely, thereby improving adherence among high-risk patients groups. In the past few decades, health IT has been applied in a number of methods to combat nonadherence:

a. Medication Event Monitoring System (MEMS) bottle caps are one intervention that provides a measure of medication adherence. These bottle caps contain special computer microchips that fit on standard medication containers. The microchips store data (date and time) each time the containers are opened and closed. The data can be downloaded and transmitted into a computer for review and analysis. Problems with the system included retrieval of the MEMS caps and the desire to hoard medicines by taking doses at different frequencies than those recorded (Kheir et al. 2010).

b. Email or SMS reminders can be used to remind patients about refills based on the prescription requirements. Mobile messages and phone call reminders have been used frequently in ARV nonadherence preventions. Weekly SMS by nurses among HIV-infected patients in Kenya reported improved adherence to ARV therapy (61.5%) compared with the control group (49.8%) (Lester 2010). Pharmacies (e.g., Walgreens in the US) provide options for patients to choose their preferred methods of reminding.

c. The Internet-based surveillance and adherence-facilitating platform MijnGezondheid.net is a Dutch patient information portal for both patients and healthcare providers to check real-time medication data, where patients can request refills online and improve adherence from a convenient online service.

d. Electronic prescriptions can increase the adherence rate of first fills for prescriptions and can also serve as reminders for refills. Electronic prescriptions were 10% more likely to be filled and picked up by patients than paper prescriptions according to a study of more than 40 million prescriptions (Information Week 2012).

For more in-depth information on the use of health informatics to improve adherence and medicine use more broadly, please refer to the Health Informatics section.

Country case studies: Brazil, Germany, Denmark

Please see the following pages for four country case studies from Brazil, Germany and Denmark. Each exemplifies a nationally-led adherence policy focused on a subset of the population with specific diseases.
**IMPROVE ADHERENCE: CASE STUDY 1 – BRAZIL**

**Brazil’s national plan improved adherence and outcomes in TB**

**BACKGROUND**

Brazil is one of the 22 high-burden countries (countries holding 80% of the TB cases of the world). In fact, TB is the fourth cause of death by infectious diseases. There were an estimated 1,056 cases of MDR-TB in 2007, but as of March 2009, XDR-TB has also been identified. Increased primary resistance to isoniazid and primary resistance to isoniazid associated with rifampicin were observed in the comparison between the II National Survey on Anti-TB Drug Resistance conducted in 2007-2008 and the results of the I National Survey, conducted from 1995 to 1997.

**INTERVENTIONS**

In 1998, Brazil adopted Directly Observed Treatment Short course (DOTS) strategy for tuberculosis treatment. In 2002, 5.2Mn USD were delegated to the program, and this increased to 74Mn USD in 2011 (Brazil Ministry of Health 2012). Brazil’s budget for TB control increased 14 times over the last nine years.

The government has also provided supportive benefits to TB patients. In the Amazonas region, for example, TB patients have free passes for public transport as a means to encourage adherence to the treatment. In São Paulo, a free meal is offered to the patients who show up to take their medication in direct observation therapy. In 2009, Brazil introduced a new system for TB treatment (fixed-dose combination or 4-in-1). This led to a reduction in the number of pills to be ingested by the patients, offering more comfort for the patient and improving the likelihood of patient adherence.

**OUTCOMES**

- Currently, 71.5% of Brazil’s health units treat TB patients using DOTS strategy.
- The case detection rate was 88% in 2010 (the WHO target is 70%).
- There was a 15.9% decrease in the incidence rate and a 23.4% decrease in mortality per 100,000 population over the last decade.
- The treatment dropout rate fell from 14% in 1999 to 9.4% in 2008-2009 and 7% in 2010 (the WHO target is 5%).
- The treatment success rate was 70.3% in 2010 (the WHO target is 85%) – this is still a challenge.

Sources: WHO 2011; Brazil Ministry of Health 2012; Brazil Ministry of Health Technical Note 2009.
IMPROVE ADHERENCE: CASE STUDY 2 – BRAZIL

Brazil’s government increased coverage and targeted interventions improved HIV medication adherence

BACKGROUND

About one-third of all people living with HIV in Central and South America live in Brazil. Untreated HIV patients have a higher viral load (and consequently an increased transmission potential) and greater risk for immune system damage, leaving them susceptible to opportunistic infections. Limited access to ARV drugs leads to nonadherence to treatment, resulting in the emergence of a virus with high resistance to the drugs, a menace that needs to be avoided.

INTERVENTIONS

Free HIV treatment has been ensured by law since 1996. Specialised Care Services (Serviço de Assistência Especializada – SAE) were introduced by the government to support medicines management for HIV patients. This programme provides multifaceted support for HIV-positive patients, including nursing care, counselling and psychological support, control and distribution of ARV drugs, educational activities for adherence, and prevention and control of sexually-transmitted diseases and AIDS. Support is also provided in multiple settings that encompass outpatient clinics, hospitals, basic health units, and polyclinics administered by municipalities, states, the federal government, universities, and nongovernmental health organisations [NGOs]. In these settings, patients can access a multiprofessional team including doctors, psychologists, nurses, pharmacists, nutritionists, social workers, and educators. These stakeholders all play a role in supporting patient adherence.

Around 600Mn USD per year is spent on HIV treatment and support.

OUTCOMES

- At the end of 2010, the proportion of the eligible population in Brazil receiving ARV therapy was 60% to 79%.
- Mortality per 100,000 population was reduced from 9.6 in 1996 to 6.4 in 1999 (a 33% decrease).
- Early and ongoing HIV prevention and treatment efforts have contained the epidemic in Brazil. The adult HIV prevalence in Brazil has remained well under 1% for at least the past decade.
- At least 90% of the patients remain on treatment 12 months after initiation.
- More than 1.2 million life-years are estimated to have been gained in Brazil between 1996 and 2009.
The following figure demonstrates the progress that Brazil has made compared to other countries with similar expenditures on health.

**KEY CAPABILITIES**

**National-level political will to make TB and HIV a priority:** Brazil declared TB an official public health priority in 2003 and has committed funds. For HIV, political will rose from civil society activism and increasing incidence since the 1980s. The government has played a role in global price reduction for ARV therapies to increase access to treatment using a three-fold strategy: investing in local producers, large-scale procurement, and price negotiations with companies that hold patent rights.

**Strong civil society:** Key NGOs (e.g., Associação Brasileira Interdiciplinar de AIDS and Grupo pela Valorização, Integração e Dignidade do Doente de Aids [Pela VIDDA]) have played a role in lobbying the government for access to treatment and services.

**Evidence-based prescribing guideline:** Guidelines encourage fixed-dose combinations for TB and attention is paid to ensure they are followed.

**Workforce investment:** It is part of the government’s strategy in the National Programme of Tuberculosis Control (Programa Nacional de Controle da Tuberculose – PNCT) to train health professionals in DOTS strategy. For HIV, the government has invested in a multistakeholder team that provides a comprehensive set of services for HIV patients.

*Life-years among adults gained due to antiretroviral therapy between 1996 to 2009 in the 25 countries with the highest number of people living with HIV.

BRA, Brazil; BWA, Botswana; CH, China; CMR, Cameroon; ETH, Ethiopia; GHA, Ghana; IDN, Indonesia; IND, India; KEN, Kenya; MOZ, Mozambique; NGA, Nigeria; RUS, Russian Federation; THA, Thailand; UGA, Uganda; UKR, Ukraine; VNM, Viet Nam; ZAF, South Africa, ZMB, Zambia.

Sources: UNAIDS 2010; UNAIDS 2011; Varella 2012; AIDSMap 2012; Nunn et al. 2009.
German pharmaceutical care: From a controlled trial to incorporation into the national guideline

BACKGROUND

Although new drugs have been developed, there have been no major changes in morbidity and mortality of patients with asthma in Germany. Correct use of inhaled medication is essential to asthma treatment effectiveness. Up to 90% of hospitalisations due to asthma are preventable, provided that patients are trained, supervised, and treated consistently. The literature shows that patients' knowledge about asthma and adherence with medication is generally poor. The Centre for Drug Information and Pharmacy Practice (ZAPP) in Germany has expertise in developing cognitive pharmaceutical care services and decided to implement a strategy to improve adherence among asthma patients.

INTERVENTIONS: A four-stage concept

Stage 1: A controlled trial conducted in 242 patients and 48 pharmacies in the city of Hamburg. Pharmaceutical service was provided to 161 patients with asthma in the intervention group and 81 patients in the control group. This involved 26 intervention and 22 control pharmacies as well as approximately 120 physicians. The findings showed that pharmaceutical care performed in community pharmacies has a positive impact on patient's asthma management and quality of life. Moreover, pharmaceutical care was demonstrated to be feasible and highly accepted by the patients as a long-term service in primary care.

Stage 2: An intervention study on the regional level conducted in 183 patients, 39 pharmacies, and 84 physicians. This stage also included collaboration with regional physicians’ associations and health insurance funds. The intervention study was based in the region of Trier, involving two of the largest statutory health insurance funds (AOK Rheinland-Pfalz and BARMER) and local physicians’ associations. This study showed that pharmaceutical care for asthma patients has a positive impact on humanistic and, to some extent, clinical outcomes.

Stage 3: In this stage, the programme was implemented nationwide into daily practice. Certified education programmes in accordance with physicians’ associations were offered by the 17 state chambers of pharmacists. Pharmacists engaged in quality circles on pharmaceutical care to monitor activities, and used special pharmaceutical software.

Stage 4: Nationwide adoption as pharmacists were invited to participate in the compilation of the National Asthma Care Guideline. The responsibility of the pharmacist for a safe and effective use of inhaled medication was incorporated into the guideline. Pharmacists also cooperated on the national level with the Federal Association of Statutory Health Insurance Physicians (KBV). Together they developed an interdisciplinary, team-based medication management concept that encourages a stronger, more active role of pharmacists and physicians in patient care. The concept has been developed to secure adequate and equal remuneration for pharmacists and physicians.
**KEY COMPONENTS OF THE INTERVENTION STUDY IN THE SECOND STAGE**

**Pharmacy preparation**

- **Pharmacist education:** At least one pharmacist in each pharmacy was trained to provide asthma service. The training was based on a nationally certificated curriculum; a manual comprising disease and therapy knowledge; communication skills; the use of the study protocol; and documentation forms.
- **Coordination:** Meetings between physicians and pharmacists were scheduled regularly to establish cooperation.

**Pharmacy service**

- **Patient education:** Patients were educated about asthma pathology, the use of asthma medication, inhalation technique, and self-management skills. At the beginning of the study, each patient was instructed to use a peak flow meter twice daily and document the results in an asthma diary.
- **Medicine use review:** When drug-related problems were detected, pharmacists discussed with physicians to solve them (e.g., modify the regimen).

**Monitoring:** Throughout the study, pharmacies were monitored by a pharmacist employed for this study. This pharmacist visited all practice sites regularly to check for compliance with the study protocol and with the documentation forms for pharmaceutical care to minimise missing data.

**Counselling:** Counselling onsite and via phone/fax was offered from the first day until the end of the study.

**OUTCOMES**

The programme improved adherence by 6% and reduced asthma severity by 15% over a 12-month period.


---

**Health outcomes improved...**

% of change after 6-month and 12-month implementation in the intervention group, 2005

- Asthma severity
- Dyspnea severity
- Asthma symptoms
- Peak expiratory flow rate

**...So did the self-management and self-efficacy outcomes**

% of change after 6-month and 12-month implementation in the intervention group, 2005

- Adherence
- Inhalation technique
- Self-efficacy
- Knowledge

---

1 Asthma severity and asthma symptoms were rated by patients, scaling from 1 to 4 and 0 to 3, respectively.
2 Dyspnea severity was also assessed by patients using Medical Research Council Dyspnea Scale.
3 Peak expiratory flow rate (L/min) was measured in the pharmacy.
4 Inflation was measured with FOTI scale (0-7).
5 Self-efficacy and knowledge data was collected from questionnaire.

---

**Continued overleaf ➡️**
Legislative outcomes were also achieved: National Programme for Guidelines. Pharmacists were invited to participate in the update process for the National Asthma Care Guideline 2nd Edition. The responsibility of the pharmacist for a safe and effective use of inhaled medication was incorporated into the guideline. Cooperation with the Federal Association of Statutory Health Insurance Physicians (KBV) led to the inclusion of pharmaceutical care in German Social Law (§ 64a SGB V) as of January 1, 2012. It is currently being tested as a concept in one region.

**OUTCOMES continued**

**KEY CAPABILITIES**

**Data collection:** Recruitment of patients in pharmacies and at GPs; clinical outcome data collection in pharmacies; patients completed self-administered questionnaires; health insurance funds provided claims data to the pharmacists to track outcomes.

**Multistakeholder engagement:** Collaboration between pharmacists, physicians, and health insurance funds forms the solid basis for countrywide implementation of the service, the incorporation of the service in the guidelines, and development of subsequent projects.

**Continuing education programmes:** Pharmacies are offered an educational programme on pharmaceutical care of patients with asthma by the 17 state chambers of pharmacists.

**Software:** Software has been developed for the implementation of pharmaceutical care in daily practice, which is an ‘add-on’ to the current software used by the pharmacies. Its main purpose was to increase working efficiency for the pharmacists conducting pharmaceutical care in daily practice.

Sources: Schulz et al. 2001; Mangiapane et al. 2005; Schulz 2012.
An inhaler technique assessment service by pharmacists improved adherence and reduced inhalation errors by 80%

BACKGROUND

In 2007, it was estimated that approximately 5.4% of the population used inhaled asthma medication. However, nonadherence to asthma medication is common, ranging from 10% to 55% in Denmark. This results in poor treatment effects, reduced quality of life, and increased costs to the health care system.

INTERVENTIONS

In 2005, the Danish government introduced the Inhaler Technique Assessment Service (ITAS) as part of Danish Asthma Therapeutic Outcomes Monitoring. The ITAS service is not only delivered by pharmacists, but also by pharmacy assistants. The Association of Danish Pharmacies offers a certification programme for all staff members who deliver the service.

**All pharmacies in Denmark are required to provide the service** to first-time users and users who demonstrate problems with inhalation techniques. The service can also be offered to chronic obstructive pulmonary disease (COPD) patients. Pharmacists use an ITAS manual developed by the Danish Association of Pharmacies describing requirements of the service. Pharmacy staff instruct patients by giving a demonstration of inhalation techniques. Then patients show the use of the inhaler by means of a placebo inhaler. Pharmacy staff assess patients’ inhalation technique, correct their errors, and document the individual elements of the inhalation technique on a special form. Counselling is provided if mistakes are observed. The service is estimated to take only 10 minutes.

OUTCOMES

- **Service coverage:** In 2011, pharmacies delivered approximately 61,280 inhaler technique assessment services. After the introduction of the service to COPD patients, the number of delivered services has grown considerably.

- **Pharmacists’ remuneration by government:** The service was the first pharmacy service reimbursed by the Danish government. The pharmacy can offer one service per patient per year and is paid 80 DKK (10.6 Euros) per service provided the service is documented.

- **Health outcomes:** In the controlled study that informed the policy, intervention patients improved their inhaler technique errors by 90% vs. control patients who improved by 30% over a 12-month period. The results were confirmed in subsequent implementation projects.

  The certification (operated by Pharmakon) is optional at present, but will become mandatory in January 2013.
KEY CAPABILITIES

**Legislation** changes to allow reimbursement of the service and recognition of pharmaceutical care as an important component of adherence interventions.

**Multistakeholder engagement**, especially participation by community pharmacists. Their availability to provide additional service is fundamental to this project.

**Data collection:** Individual elements of patients’ inhalation techniques are documented on a form during assessment. The documented forms are used to claim reimbursement.

**Information materials** such as brochures to patients, letters to physicians, and local press releases are utilised.

*Sources: Herborg et al. 2001; Herborg 2012.*
Background analysis

There are volumes of material on the subject of nonadherence, interventions, and recommendations. This section is by no means exhaustive, but highlights specific topics chosen to be most relevant for this audience in the scope of this report.

**CONTEXT: DEFINING THE PROBLEM**

Adherence to medicines is defined as the extent to which the patient’s action matches the presumably agreed recommendations by the healthcare providers (National Institute for Health and Clinical Excellence 2009). Failure or refusal to follow the recommended regimen can be seen as poor adherence or nonadherence. Behaviours of adherence or nonadherence to a regimen can be tracked when a patient seeks medical treatment, fills prescriptions, takes medication appropriately, attends follow-up appointments, and executes behavioural modifications that address health issues (World Health Organization 2003a).

**ADHERENCE, COMPLIANCE, OR PERSISTENCE?**

This report uses the term ‘adherence’ which originally evolved from ‘compliance’. The latter implies involuntary submission to authorities, whereas adherence refers to an act of voluntarily subscribing to a point of view (Stone et al. 1998). The variety of terminology used in reference to understanding how patients take their medicines reflects the language evolution from a physician-led to a patient-centric approach. It also indirectly reflects the methods with which researchers collect relevant data. While adherence and compliance measure the extent to which the patient acts in accordance with the prescribed interval and dose of a dosing regimen, persistence is the duration of time from initiation to discontinuation of therapy. Studies at IMS Health measured adherence through the proportion of days covered (pDC), calculated as the number of days with medicine on-hand divided by the number of days in the given time interval. This reflects both compliance and persistence. Nevertheless, debates and research developments continue to identify appropriate definitions and measurement methods (ISPOR Medication Compliance and Persistence Working Group 2009).

**Methodological challenges in research:** There are two methodological challenges in understanding the scale of nonadherence as a problem. The first challenge is related to how nonadherence is defined. Some studies use the percentage of remaining pills to calculate nonadherence; other studies use Medication Possession Ratios (MPRs), the proportion of days that patients are on medication given the researched period. Even in studies using MPRs, the adherence level is set under different MPR rates. Persistence, on the other hand, is a dichotomous yes or no measure that is based on the length of therapy and tells whether the patient’s length of therapy meets or exceeds a certain threshold. Defining thresholds can be a challenge. An example where an adherence level is consistent and has proven to improve outcomes is with HIV. Among HIV-positive patients on ARV therapy, 95% adherence to therapy is a widely accepted minimal level of adherence necessary to maintain an HIV load suppression of <400 copies/mL in the majority of individuals. This maintains a certain level of viral load suppression and prevents emergence of medicine resistance (APHA 2004; Rosenblum et al. 2009). For most NCDs there is limited conclusive evidence on what the right threshold should be, and this warrants continued research.

The second challenge is related to limitations of research relying on patient self-reported adherence. Research shows that patients overstate adherence levels and consequently the use of other approaches is critical. Correlating questions about patient behaviours with prescription and other medical claims data and with drug-cap devices improves the accuracy of results. For example, adherence with CV medication is remarkably lower with this approach vs. using self-reported patient information alone (Tierce 2011). It is important to note these research challenges when assessing adherence-related material.

**EXISTING PREVALENCE**

Poor adherence is a worldwide problem of remarkable magnitude and is particularly common among patients with chronic diseases. In developed countries, adherence to long-term therapy for chronic illnesses averaged only 50% (World Health Organization 2003a). In fact, adherence rates do not seem to vary between developed and developing countries. Instead, the drivers
WHY DOES NONADHERENCE OCCUR?

The risk factors for nonadherence interact with one another and differ depending on the surrounding circumstances such as the economy and health system structures. Therefore, it is impossible to gauge which factors, in silo, are drivers for nonadherence.

Risk factors for nonadherence:

• **Demographic:** Age (e.g., elderly patients tend to be more forgetful in taking medicines), education (which affects health literacy), culture (a study among students found that those with Asian backgrounds were significantly more likely to intrinsically perceive medicines to be harmful than those of European origins), religion (medicine is forbidden), or general dislike of and mistrust in medicines (e.g. a dislike of taking medications on a long-term basis, and uncertainty about the need for treatment) are predominant patient-reported reasons for discontinuation (Goldberg et al. 2009).

• **Economic:** Economic factors compounded by patients’ income level and available resources in the health system affect patients’ likelihood of adherence. This is particularly prominent in low-income countries with low reimbursement and in high-income countries with high out-of-pocket spending (e.g., copayments). Transport access may also be a risk to adherence if patients do not have the means to travel and obtain medicines.

• **Social:** Positive family or community support in treating HIV and diabetes has a significant impact on medication adherence. Adherence of children with asthma is largely dependent on consistent monitoring and care from their family (World Health Organization, 2003a).

• **Nature of illness:** Adherence rates vary widely depending on whether the disease is acute or asymptomatic but chronic and whether patients have comorbidities. For example, the DAWN study showed that patients with diabetes also tend to have poor psychological well-being, and this has a negative impact on medicine adherence (Funnell 2006). Depression is one of the most common diseases associated
with other chronic diseases, and has been shown to be associated with nonadherence in patients with diabetes, hypertension, and HIV (Gonzalez et al. 2008; Lin et al. 2004; Gonzalez et al. 2011).

- **The relationship between the patient and healthcare professionals:** The relationship between patients and healthcare professionals (including clinicians and pharmacists) influences the patient’s commitment to their regimens. Collaborative communication was associated with high adherence rate in a study among American low-income patients with hypertension (Schoenthaler et al. 2009). Existing evidence showed that doctors rarely discuss with patients their ability to follow a treatment plan (Elwyn et al. 2003).

- **Patient and product suitability:**
  - Inappropriate device/packaging: Patient satisfaction with treatment devices or medication packaging is an indicator for compliance. In asthma treatment, the type of inhaler device appears to be associated with adherence to asthma control medications (Roy et al. 2011). Also, the higher the level of satisfaction that the patient reported for their device, the more likely the patient was to be adherent and experience better outcomes, including quality of life (Small et al. 2011). Reminder packaging (which incorporates a date or time for a medication to be taken in the packaging) showed a significant increase (11%) in the percentage of pills taken (Heneghan et al. 2006).
  
  - Complexity of the treatment regimen: Including the number and kinds of medicines to be taken each time, the duration of therapy, and the dosing frequency is a predictor of medication adherence. HIV patients with simpler regimens reported better adherence rates than those with complex ones (Stone et al. 2001). An analysis in Figure 6 done by IMS Health using longitudinal patient data for the UK also showed that medication taken once daily has better adherence than medication taken twice daily.

- **Adverse effects:** Adverse effects are a major contributor to nonadherence in antituberculosis treatment (Awofeso 2008). Cancer patients may discontinue medication when they experience serious adverse effects, such as nausea, vomiting and diarrhoea. Adverse effects also affect adherence in ARV therapy in persons with HIV infection (Ammassari et al. 2001; Stone et al. 2001) and antihypertensive medications in patients with hypertension (Dusing et al. 1998; Stone et al. 2001).

- **Other factors:** Past adherence is also a good positive predictor for adherence. The strongest predictor seems to be the duration of therapy. Longer duration decreases the likelihood of maintained adherence.

![Graph showing the relationship between time per day and percentage of patients retained on treatment](source: IMS UK Disease Analyser, 2004.)

**FIGURE 6: REDUCING TIME PER DAY INCREASES PERCENTAGE OF PATIENTS RETAINED ON TREATMENT**

<table>
<thead>
<tr>
<th>Months from initiation</th>
<th>Once daily</th>
<th>Twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 1</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>1 to 2</td>
<td>80%</td>
<td>60%</td>
</tr>
<tr>
<td>2 to 3</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>3 to 4</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>4 to 5</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td>5 to 6</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>6 to 7</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>7 to 8</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>8 to 9</td>
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<td>0%</td>
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<tr>
<td>9 to 10</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>10 to 11</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>11 to 12</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Health system approach not tailored to patients with chronic NCDs: As mentioned above, patients with chronic diseases that are primarily asymptomatic (especially in the early stages) are at high risk of nonadherence. From a care and quality perspective, health systems have historically focused on patients with acute rather than chronic conditions. Patients with chronic conditions need care that is delivered by a healthcare team (rather than one or two types of doctors) integrated across care settings that supports self-management (Ham 2010). In fact, patient-centred, chronic disease self-management programmes have been shown to improve disease control and patient satisfaction through improved medicine intake and general care (Stec-Alt and Schatell 2008). The delay in adaptation to a new paradigm that caters to chronic disease patients is slow and, though indirect, contributes to nonadherence levels.

It is important to note that sometimes patients simply refuse to take their medication even though they are aware of the importance for improved health outcomes. In some cases, patients stop taking medicines because they experience improvement and feel the medicines are no longer needed. Human behaviour cannot be 100% controlled, so there will always be some level of nonadherence among most patients. Clinicians and pharmacists work in an uncertain environment in which they are unable to control for most of these factors.

Figure 7 summarises the risk factors associated with nonadherence and their relationship with pharmacists, clinicians, and patients.

**FIGURE 7: HEALTHCARE PROFESSIONALS’ ABILITY TO MANAGE PATIENTS’ MEDICINE USE AND PATIENTS’ BELIEF SYSTEMS IN LIGHT OF NONADHERENCE RISK FACTORS**

How can clinicians and pharmacists be best prepared to minimise nonadherence?

- **PHARMACISTS**
  - Healthcare professionals have limited control when it comes to nonadherence risk factors

- **CLINICIANS**
  - How can clinicians and pharmacists be best prepared to minimise nonadherence?

How can patients’ belief systems be responsive to medicine adherence?

- **PATIENTS**
  - Nonadherence risk factors drive patients’ belief systems, responsiveness, and ability to adhere

<table>
<thead>
<tr>
<th>Nonadherence risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Demographics (e.g., age, race)</td>
</tr>
<tr>
<td>✓ Economics (e.g., affordability, transport)</td>
</tr>
<tr>
<td>✓ Social (limited family/friend support)</td>
</tr>
<tr>
<td>✓ Nature of disease (chronic, multiple)</td>
</tr>
<tr>
<td>✓ Relationships between patient and healthcare professionals</td>
</tr>
<tr>
<td>✓ Patient and product suitability</td>
</tr>
</tbody>
</table>

Both healthcare professionals and patients must have a strategy to start right when medication is first provided and then maintain adherence after initiation.
IMPACT ASSESSMENT

Economic burden

Countries pay excessively for avoidable costs caused by nonadherence. In the US, excess hospital admissions were estimated to be more than 100Bn USD per year by nonadherence, which represented 5.0% of total health expenditure (Osterberg and Blaschle 2005; National Pharmaceutical Council 1992). In the UK, avoidable costs are estimated as much as 5Bn GBP in 2009, including medicines not used correctly or not used at all and avoidable hospital admissions. This equates to around 4% of total health expenditure. An analysis by the National Audit Office in 2007 suggests that wasted medicines in primary care were estimated to be worth 800Mn GBP. Approximately 1.5Mn GBP was spent across England by primary care trusts on destroying returned medicines (National Audit Office 2007).

The economic costs go beyond avoidable costs of medicines and include costs arising from increased demands for healthcare if the patient’s condition deteriorates. Sokol et al. conducted a study in 2005 on the impact of medication adherence on healthcare utilisation and costs for four chronic diseases, including diabetes. This study concluded that a high level of medication adherence in diabetes was associated with lower disease-related costs. This study also showed that hospitalisation rates were lower in patients who were more adherent to their regimens (Dusing et al. 1998; Sokol et al. 2005).

In the US, medication nonadherence is considered to be the cause of 33% to 69% of medication-related hospital admissions, 23% of all nursing home admissions, repeat visits to doctors, ED visits, and related loss in productivity. Among patients with type 2 diabetes, those with a low level of adherence cost the health system 16,898 USD per person annually, 90% more than patients with high adherence. Similar studies on hypercholesterolemia represented a 60% difference on total health cost (Sokol et al. 2005).

Other studies found adherence is a predictor of health care cost. For instance, increased adherence to antidiabetic regimens represented an 8.6% to 28.9% decrease in annual costs with every 10% increase in MPRs. Adherence to antidiabetic medications was a great driver of cost reduction (Balkrishnan et al. 2003; Sokol et al. 2005).

Worse outcomes

Past research across different diseases demonstrates direct correlation between adherence rates and improved health outcomes.

- Nonadherence is one of the chief causes of treatment failure in typical HIV patient care settings, where ARV regimens have high pill burden, dietary restrictions and complicated dosing schedules (Munakata et al. 2006).
- Low adherence with five antihypertensive drug classes (angiotensin II receptor blockers, ACE-inhibitors, β-blockers, calcium channel blockers and diuretics) and first event of hypertension (e.g., stroke) have been shown to be linked (Mathes et al. 2010).
- Among statin users, the risk of mortality was greatest for low adherers (24%) compared with high adherers (16%). A similar but less pronounced dose-response type adherence-mortality association was observed for beta-blockers (Rasmussen et al. 2007). Improving adherence with medications that manage risk factors of cardiovascular disease (CVD) has been shown to reduce cardiovascular events, including the risk of recurrent myocardial infarction (MI) and stroke, rehospitalisations, and all-cause mortality. Large randomised controlled trials and meta-analyses have identified several lifesaving medicines for CVD patients. Nonadherence to these medications resulted in death and huge health care cost. The risk of a recurrent stroke is 30% to 43% within five years in the UK, which could be much lower if adherence to these medicines is maintained (O’Carroll et al. 2010).


Brazil Ministry of Health 2010. [Changes in tuberculosis treatment]. Rev.Saude Publica, 44, (1) 197-199


References continued


DiMatteo, M.R. 2004. Variations in patients’ adherence to medical recommendations: a quantitative review of 50 years of research. Medical Care, 42, (3) 200


Heneghan, C.J., Glasziou, P., and perera, R. 2006. Reminder packaging for improving adherence to self-administered long-term medications. Cochrane Database of Systematic Reviews (1) CD005025

Herborg, H. Personal communication with Hanne Herborg, Pharmakon Denmark, Denmark. Apr., 2012.


Le Pen, C. Personal communication with Claude Le Pen. May 3, 2012


References continued


References continued


Roebuck, M.C., Liberman, J.N., Gemmill-Toyama, M., and Brennan, T.A. 2011. Medication adherence leads to lower health care use and costs despite increased drug spending. Health Affairs, 30, (1) 91-99


Schneider, J., Kaplan, S.H., Greenfield, S., Li, W., and Wilson, I.B. 2004. Better physician-patient relationships are associated with higher reported adherence to antiretroviral therapy in patients with HIV infection. Journal of General Internal Medicine, 19, (11) 1096-1103


Schroeder, K., Fahey, T., and Ebrahim, S. 2004. Interventions for improving adherence to treatment in patients with high blood pressure in ambulatory settings. Cochrane Database of Systematic Reviews (2) CD004804

Schulz, M. Personal communication with Martin Schulz, ABDA - Bundesvereinigung Deutscher Apothekerverbände, Germany. Apr., 2012


References continued


Van Dijk, L. Personal communication with Liset Van Dijk, NIVEL. 2012


IV. Medicine use revisited: Six primary levers of opportunity

2. RIGHT MEDICINE TO THE RIGHT PATIENT

Ensure timely medicine use

Untimely medicines use contributes 13% of the world’s total avoidable cost due to suboptimal medicine use.
2. RIGHT MEDICINE TO THE RIGHT PATIENT: ENSURE TIMELY MEDICINE USE

Untimely medicines use contributes 13% of the world’s total avoidable cost due to suboptimal medicine use.

A total of 1.1% of global total health expenditure (THE), or 628bn USD worldwide, can be avoided if timely treatment is provided.

The analysis and quantified magnitude in this section is based on a communicable and noncommunicable disease focus: timely treatment of hepatitis B and hepatitis C to prevent liver cancer and cirrhosis, and type 2 diabetes to prevent cardiovascular and cerebrovascular complications. Figure 8 below provides a snapshot summary of the relative avoidable costs out of THE.

Data and respected ranges were estimated based on a combination of estimated and real values as well as data reliability. Where there are only two points, the point estimate is the minimum. Global average values are weighted by country total health expenditure. Countries vary primarily by a combination of infrastructure, affordability, and noncommunicable disease risk factors. This explains why Japan and France are relatively lower compared with the US and the UK. Most low-income countries experience greater avoidable spending from untimely use since diagnostic capabilities are limited given weak infrastructure.

Ministerial relevance and recommendations

• NCDs can be prevented and managed with better medicine use to prevent costly complications that require hospital-based care and treatment:

FIGURE 8: AVOIDABLE COSTS (% OF THE) AT THE COUNTRY LEVEL

Source: IMS MIDAS, 2009 and 2011; World Bank 2009; WHO 2009; USD in 2011; Please see methodology section for details on global calculations which include 186 countries
### RECOMMENDATIONS: TIMELY TREATMENT PROVISION IN CERTAIN DISEASES CAN IMPROVE MEDICINE USE: HBV, HCV, AND TYPE 2 DIABETES

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<thead>
<tr>
<th>POTENTIAL MOH INTERVENTIONS</th>
<th>REFERENCE POINT</th>
<th>SPEND</th>
<th>HEALTH OUTCOME</th>
<th>TIME SCALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure surveillance systems are in place for costly diseases that can be prevented through cheap, timely interventions</td>
<td>UK (HBV, HCV), Australia (Diabetes)</td>
<td>High cost</td>
<td>Medium</td>
<td>3-5 years</td>
</tr>
<tr>
<td>Conduct economic evaluation study to determine whether a screening and treatment programme would be optimal for either the population or specific high-risk groups</td>
<td>Thailand (HITAP)</td>
<td>Moderate cost</td>
<td>Medium</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Support targeted disease management programmes for prevalent noncommunicable diseases such as diabetes to ensure timely therapy initiation: not for all patients but for those at highest risk</td>
<td>US (The Southern California Permanente Medical Group diabetes care), Germany diabetes management programme</td>
<td>Moderate cost</td>
<td>Medium</td>
<td>2-3 years</td>
</tr>
</tbody>
</table>

- Hepatitis B (HBV) and hepatitis C (HCV) are responsible for cirrhosis and hepatocellular carcinoma, one of the leading causes of cancer worldwide.
- Patients with type 2 diabetes are twice as likely to have complications such as stroke and myocardial infarctions.
- Ministers of Health can use political will to encourage disease management for patients with high risk factors. This is critical to identify patients early and treat them with medicines to prevent more costly, downstream expenses (often costlier than medicines themselves).

**Basis for recommendations: Interventions and policy options overview**

‘Right medicines to the right patient’ needs to happen at the ‘right’ time so that patients receive medicines when they are most likely to maximise outcomes in a targeted way and minimise disease severity. One of the more obvious ways to ensure that this happens is through preventative medicines such as vaccines. Regular screening and diagnosis for specific diseases may also, albeit indirectly, affect responsible medicine use, although population-based efforts are controversial and do not obviously save costs or improve health outcomes. For example, cost-effectiveness of cervical cancer screening would arise from a simplified screening process that minimises the number of false-positive results (van den Akker-van Marle 2002). Any population-based screening programme carries trade-offs and complexities related to resource implications, number needed to screen to identify one patient for treatment (the more needed, the more expensive it is), and the likelihood of false-positive or false-negative results.

Another key factor in timely interventions is public health-related interventions that prevent onset of disease through risk factor mitigation. For example, discouraging smoking and/or alcohol consumption, encouraging healthy diet and food intake, as well as regular physical exercise are common ways to prevent onset of some of the main NCDs discussed throughout this report. While the importance of these issues and related interventions is recognised, the focus on public health in this report is limited given the indirect implications on medicine use.
In this section, the importance of early screening and diagnosis is highlighted in specific diseases that have direct implications on medicine use. The first disease focus is hepatitis B and C which are communicable diseases. The second is diabetes type 2. In both cases, patients should take medicines at the right time at specific points in the disease pathway to prevent another disease or worsening of the existing disease. While detailed analysis is not provided, untreated atrial fibrillation (AF) is another example of a condition that can be managed through early identification and treatment to avoid stroke. AF increases the risk of stroke five times over the general population; 15% of strokes are a result of untreated AF yet most people do not know what it is (American Heart Association 2011).

Hepatitis B & C focus

Treatment in the early stages of HBV and HCV has been proven to be incrementally cost-effective in several studies, particularly among high-risk groups such as migrants (See the Thailand case study) (Kanwal et al. 2006; Veldhuijzen 2010). Screening for both diseases is required to detect cases early. Early HBV and HCV treatment can prevent late-stage complications, improve health, and reduce premature death. Hence, it has been proven to be highly cost-effective in as little as ten years (Post et al. 2011; Eckman et al. 2011).

It is important to note that while HCV does not yet have a vaccine, universal HBV vaccination has been shown to save money and lives (WHO Hepatitis B/Fact Sheet VHPB/1996/1). While such a vaccine has existed for more than 20 years, global control of HBV has not yet been achieved. Consequently, besides vaccines, efforts to diagnose and treat early are also crucial.

The most common intervention for HBV and HCV would be a screening-based programme that would identify chronic patients early to provide those with a potential chance of liver damage with antiviral treatments such as Viread® (tenofovir) or Baraclude® (entecavir) for HBV and interferons and ribavirin (there are a number of branded products) for HCV. Indeed, early treatment can improve outcomes and offset costs from complications that can be prevented. Screening for HBV and providing early care helps improve health outcomes in the short and long term. The proportion of HBV patients with resolved infections or low viral loads was 52.5% in the late care scenario vs. 80.0% in the early care scenario after just five years of treatment vs. lack of treatment (Post et al. 2011). Screening and early diagnosis can also greatly reduce mortality rate: rates of death per 100,000 were 2,094 in late care, while in early care they were only 1,628. After 20 years, the cumulative mortality rates for late and early care scenario were, 20,730 and 11,606 per 100,000 respectively (Post et al. 2011).

For HCV, diagnosing patients early can lead to improved treatment response, lower viral loads, decreased progression to cirrhosis, and prevention of hepatocellular carcinoma (Senadhi 2011). A recent study suggested incorporation of universal screening into national guidelines given public support and patient priorities (Coffin et al. 2011). Current therapies achieve about a 50% cure rate, and broad implementation could reduce HCV complications by 16% to 42%.

From a cost or economic burden perspective, cost-effectiveness has been demonstrated in some studies. The implication for a ministerial audience is to invest in a local cost-effectiveness or other type of economic evaluation study to determine if population-based screening and treatment would be cost-effective. Economic modelling of the impact of HBV screening in the US suggested that screening for high-risk populations might be cost-effective, but not necessarily cost saving given the increased costs in screening. When treatment is given for a specific population such as pregnant women, the cost-saving element depends on perinatal transmission threshold. If the reduction in transmission is less than 18.5% then lamivudine treatment is not cost saving, but otherwise it could be. For each 100 pregnant women treated, 9.5 cases of chronic HBV infections are prevented and cost savings amount to 5,887 USD per patient with 1.2 life years gained (Unal et al. 2011). Approximately 1% of liver-related deaths would be averted per 15% of the general population screened for HCV in the US (Coffin et al. 2011).

Similar results have been found for HCV in other parts of the world. Helsper et al. reported in 2012 that targeted HCV screening for hard drug users was cost-effective in the Netherlands (Helsper et al. 2012). In the UK, screening for HCV among injection drug users would be cost-effective.
Diagnosing patients early can lead to improved treatment response, lower viral loads, decreased progression to cirrhosis, and prevention of hepatocellular carcinoma.

users was also found to be moderately cost-effective (Stein et al. 2002). Evidence for such studies is usually determined by a number of factors including acceptability, cost of screening, and adherence to treatment. Countries with high prevalence rates should conduct studies locally to determine what is most appropriate: either a targeted approach or population-based approach. A recent economic evaluation in Thailand by The Health Intervention and Technology Assessment Programme (HITAp) has led to a nationwide screening and treatment programme for both HBV and HCV patients (See the Thailand case study).

Many countries have implemented screening programmes targeting specific high-risk patients based on the notion that diagnosing these patients early can lead to improved treatment response, lower viral loads, decreased progression to cirrhosis, and prevention of hepatocellular carcinoma (Senadhi 2011).

In the US, for HBV, the US Preventive Services Task Force (USpSTF) strongly recommends screening for HBV infection in pregnant women at their first prenatal visit, but recommends against routinely screening the general asymptomatic population for chronic HBV infection (USpSTF 2009). For HCV, current US guidelines recommend limiting HCV screening to high-risk individuals (USpSTF 2004).

In the UK, the National Screening Committee (UK NSC) suggested that HBV screening should be offered to all pregnant women (Health Protection Agency Centre for Infections 2009). HCV screening is offered to high-risk groups as well, including injecting drug users and patients who have had blood transfusions during specific years (National Health Service-UK 2009). The Health Protection Agency (HPA) specifically identified South Asians at increased risk of infection, encouraging doctors to consider testing based on specific risk factors in this population (Health Protection Agency 2009).

In Australia, the Government Department of Health and Ageing established a national policy on HCV screening tests in 2007 (Australian Hepatitis C subcommittee of the Ministerial Advisory Committee on AIDS Sexual Health and Hepatitis 2007). Testing is not done without a full assessment of relative risks and benefits so the focus is on specific patients (e.g., drug users) as in the UK. In 2010, Australia also implemented a national strategy for HBV whereby screening is encouraged for priority populations as well, particularly for unvaccinated adults at higher risk of infection, such as men who have sex with men, sex workers, and injection drug users (Australian Government Department of Health and Ageing 2010).

In France, screening programmes have become successful achievements of France's HCV prevention and control programmes. It is estimated that by the year 2002, approximately 60% of new HCV patients had been diagnosed and treated following HCV screening. HBV is addressed through risk-group interventions, similar to other countries mentioned (Viral Hepatitis Prevention Board 2005).

The intervention countries take should vary depending on the in-country prevalence, and whether or not it is cost-effective or cost saving largely depends on local modelling efforts. What is known is that treatment can improve outcomes and save costs in a chronic patient's lifetime. Every 1 USD spent on combination therapy in HCV can result in about 4 USD of medical cost savings, including present value considerations and total payments for medical care (Anemia Institute for Research and Education 2005).

There is some evidence that public awareness programmes to encourage people to get screened have worked to improve outcomes. The “Face It Campaign” in the UK in 2007 led to an increase in the general public knowing about HCV (19% increase in awareness over four years after one-year intervention), testing at GP clinics, and reported infections (All-Party Parliamentary Hepatology Group 2007). Limited research exists on this subject given that most countries focus on HBV vaccination, and HCV efforts should be linked with existing treatment.

Country case study: Thailand

Thailand's Health Intervention and Technology Assessment Program (HITAP) exemplifies a successful, nationally-led initiative to assess the value of hepatitis B and C screening and treatment to save costs and improve outcomes.
Thailand applies evidence-based policy to improve screening and medicine use decisions

BACKGROUND

Hepatocellular carcinoma is the leading cancer in Thailand, causing ~20,000 deaths per year in the Thai population due to a high prevalence of chronic HBV and HCV. Each case costs 500,000 Thai baht (~16,000 USD) to treat. Active screening for HBV/HCV was not promoted or implemented by the National Health Security Office (NHSO). Despite lamivudine being available on the national medicines list, HBV/HCV patients rarely accessed it. One of the challenges has been that decision makers were historically unconvinced about the value of screening and treatment from a value for money and feasibility perspective.

INTERVENTIONS

In 2010, academics suggested that screening and treatment should be considered for use. They made a case that lamivudine should be: encouraged for use among HBV patients; introduced as second-line use for those resistant to tenofovir; included in Universal Health Coverage. Thailand’s Health Intervention and Technology Assessment Program (HITAP) initiated a model-based economic evaluation using literature, local data, and validation from relevant experts and stakeholders including physicians, patient representatives, and industry. After almost one year, results revealed that screening and treatments for chronic HBV/HCV are cost-saving for the Thai society and feasible for national implementation.

OUTCOMES

- NHSO is now subsidising HBV/HCV screening in hospitals; the NHSO has negotiated with industry to reduce the test price.
- Screenings are offered to the population free of charge in public hospitals; clinical guidelines, monitoring and evaluation, as well as financial incentives for physicians enforce regular screening.
- Lamivudine is provided as first-line therapy to HBV patients; tenofovir is included in the national medicines list as second-line treatment; pegylated interferon alpha 2a or 2b combined with ribavirin are recommended and provided for treatment of chronic HCV.
- The National Health Security Office successfully negotiated treatment prices down by more than 50%.

Treatment is now provided throughout the country and is expected to increase average life expectancies of patients by around eight years for HBV patients and four years for HCV patients. Additionally, this treatment will save 17,000 to 150,000 Thai baht (or ~539 to 4761 USD, 2011) per screening respectively.
**National political will to apply evidence-based policymaking:** The NHSO has recently demonstrated commitment to using evidence-based methods in reimbursement decisions for available treatments. The NHSO invested in HITAP in 2010 to do this research and inform medicine reimbursement and usage decisions for this specific problem based on local data and societal value. The evidence via an economic evaluation and budget impact analysis was the main tool used in industry negotiations to reduce prices. This research is one of many efforts by HITAP to apply evidence in coverage decisions. Since the Ministry of Health invested in HITAP, cost savings from decisions have already more than paid off HITAP’s annual operating costs. Additionally, there were improved health outcomes in terms of deaths averted and infections reduced.

**Diverse stakeholder engagement:** Regular dialogue with key opinion leaders in scientific disciplines to inform HTA assessment.

**Dissemination of information through online technology:** The NHSO invested substantially in information technology to inform physicians in medicine provision guidance between first- and second-line treatments.

Sources: Health Intervention and Technology Assessment Program (HITAP) 2010; Teerawattananon 2012; Tantivess et al. 2012.
Background analysis

CONTEXT: DEFINING THE PROBLEM

HBV and HCV are major causes of chronic liver diseases worldwide, which lead to cirrhosis and hepatocellular carcinoma, both severe and costly to treat. People with chronic HBV/HCV infections are communicable and are therefore serious public health risks. Both diseases are a challenge, particularly in low- and middle-income country settings.

HBV AND HCV HAVE SIMILAR CHARACTERISTICS:

• They are both responsible for cirrhosis and hepatocellular carcinoma, which is one of the leading causes of liver cancer death around the world.

• Both have a long latent phase that causes little or no clinical symptoms; their asymptomatic nature contributes to lack of (or late) diagnosis. Complications develop after years of carrying the infection. HBV/HCV carriers are unaware of this and transmit the disease to others. Although little data is available with regard to the number of undiagnosed individuals with chronic HBV infection, there is some evidence that the figures are not minimal. A study in the US that conducted HBsAg testing among Asian-born people indicated that about one-third of the infected population was unaware of their infection (Post et al. 2011). For HCV, it is believed that only 5% to 50% of infected adults in the US and Canada were thought to know their status of infection (Jafari et al. 2010). A recent study estimated that 50% to 75% of infected persons in the US remain unaware of their status (Coffin et al. 2011).

• Infection transmits mainly through blood-to-blood contact and risk-groups are similar: high-risk populations necessitate such screening. This population includes pregnant women, newborn infants whose mothers are HBV-positive, household contacts and sex partners of HBV-positive people, injection drug users, people born in regions with high HBV prevalence, and people who are the source of blood or blood fluid exposures that might require postexposure prophylaxis (Weinbaum et al. 2008).

• There are millions of carriers worldwide. For HBV, the WHO estimated that about 2 billion people worldwide have been infected with HBV and about 350 million live with chronic infection. An estimated 600,000 people die each year due to the acute or chronic consequences of HBV (WHO 2008). For HCV, there are about 170 to 200 million infected individuals worldwide with four million carriers in Europe and three to five million in the US (Dartmouth Medical School 2012). In the Eastern Mediterranean region of the world, 75% of cirrhosis and hepatocellular carcinoma was attributable to HBV or HCV, most acquired in healthcare settings (World Health Organization Regional Committee for the Eastern Mediterranean 2009).

• Both have serious complications: For HBV, it is estimated that about 15% to 40% of infected individuals will develop serious complications such as liver cancer and other end-stage liver disease. Despite the increasing availability of new treatments for HBV and HCV, they are expensive, and those for HCV are more likely to be curative. The total direct and indirect annual cost burden of HBV infection in the US is estimated to be 18bn USD (Post et al. 2011). About 15% to 20% of those with chronic HCV will develop cirrhosis within a five-year period, although the risk of liver cancer is uncertain. Nevertheless, about one-third of liver transplants in the US are due to HCV (Dartmouth Medical School 2012). In the UK, the percentage of first liver transplants due to HCV-related disease increased from 10% in 1996 to 21% in 2008 (Health Protection Agency Centre for Infections 2009).

IMPACT ASSESSMENT

Besides severe health outcomes as described above, the HBV/HCV challenge is significant from an economic perspective. Assuming an estimated survival of 25 years, the annual healthcare costs for the affected US population with chronic HBV is 360Mn USD (Dartmouth Medical School 2012). Assuming an estimated survival of 40 years, the annual healthcare costs for the affected US population with chronic HCV may be as high as 9bn USD (Dartmouth Medical School 2012). In South Korea, a study found that 632.3Mn USD (1997) were associated with HBV disease-related medical costs, every 1 USD spent on combination therapy in HCV can result in about 4 USD of medical cost savings, including present value considerations and total payments for medical care.
equivalent to about 3% of total national health expenditures at that time (Yang et al. 2001). While the economic burden of HBV has not been estimated in Canada, total HCV healthcare costs amounted to ~431Mn USD in 2005 (Dinner 2005). In Australia, total treatment costs of HCV in 2004/2005 were about 58Mn USD in 2005 (Applied Economics Pty Ltd 2005). The variability in costs is likely attributable to the different ways in which studies calculate such estimates, given that different proportions of the population would be more or less likely to have complications or liver cancer, which is the greatest part of the cost. Differences can also be attributable to variations in treatment availability and costs.

Diabetes type 2 focus

This section focuses on interventions policymakers should consider to ensure the right medicines are provided at the right time.

This research recommends three main interventions for Ministers of Health based on country examples.

1. Invest in a patient registry system to identify the appropriate and specific patient groups for therapy (e.g., insulin or other) in a timely manner.

A patient registry system records patients’ personal health records and monitors their outcomes and treatment patterns regularly. As patients’ conditions are closely tracked, the registry system largely facilitates the identification of patients whose glucose levels are at the threshold for insulin therapy. This system was demonstrated to be associated with improved diabetes care and clinical outcomes (Pollard et al. 2009; Ortiz et al. 2006). Australia is an example of a country that has had a National Patient Registry for diabetes (NDR) as part of its overall National Diabetes Service Scheme (NDSS), since 1987. It includes people who began using insulin for management of diabetes since 1 January 1999 and consented to be included in the NDR (Australia National Diabetes Register 2012). Guidance is provided for physicians and nurses on the importance of tracking patient information and using it to target interventions for improved outcomes, such as appropriate insulin use. Data analysis tools and clinical pathways for coordinated care are provided for healthcare practitioners to understand quality of practice-level data and relevant interventions (Australia Government: Department of Health Ageing 2010). It is worth noting that registry creation should include consideration of various criteria and not just HbA1c levels. While it is common to use them as a cut-off method, registries may not capture the appropriate number of patients who would benefit from early insulin usage. Therefore, registries should capture other types of information such as present comorbidities (Hellman 2012).

2. Implement a disease management programme (DMP) for diabetes patients.

Having been promoted for over a decade, initial experiences with DMPs were not all optimal. Only some programmes have demonstrated success as timely interventions with improved outcomes, such as the Germany’s diabetes DMP. This research supports the notion that DMPs target patient groups with specific outcomes (e.g., glucose levels above certain thresholds) rather than the broad diabetes population.

Germany’s diabetes DMP: In the light of a reform to strengthen chronic disease management, a diabetes management programme was introduced in 2003 in Germany on a national basis. The German Social Code Book V (SGB V) legislation defined the DMP components. One component was the treatment strategy based on the latest developments in medical science, including an insulin initiation indication (Nolte et al. 2008). By 2009, the programme had enrolled more than three million patients and significantly enhanced the quality of care for type 2 diabetes as reported by enrolled patients (Schafer et al 2010). It also reduced the incidence of some complications. New cases of foot problems after enrolment dropped 65% over six months, and lowered the overall cost of care by 13% (Brandt et al. 2010).

In France, diabetes treatment is guided by evidence-based protocols on a range of interventions in the course of disease progression, such as dietary recommendations, insulin treatment, and foot care. The indication of insulin treatment is set when maximal oral antidiabetic drugs fail to work. Chronic disease management and patients’ quality of life were
identified as among the top five priorities for the French public health policy in 2004 (Bras et al. 2006).

The UK has also implemented diabetes disease management initiatives, including some regionally-based programmes whereby insulin therapy is initiated in primary care rather than in inpatient settings.

3. Provide fast-track insulin therapy

When patients with type 2 diabetes are identified for insulin initiation there is often a delay in receiving the treatment, primarily due to the traditional request for a hospital-based specialist to decide insulin regimen and a lack of sufficient knowledge in primary care on how to prescribe and instruct insulin use. The UK has some experience in setting up such initiatives. A fast-track nurse-led service clinic for diabetic care in Leicestershire enabled nurses to treat type 2 diabetes to avoid waiting lists and prevent therapy delay. These are diabetes specialist nurses trained to determine insulin type and to calculate the dosage alleviating physicians’ time spent providing insulin. A programme audit after one year demonstrates a 2.4% mean reduction in HbA1c since referral and average waiting times reduced to 14 days from 13 weeks. Learnings include ensuring the patient is aware of the fast-track programme and prepared and mandated for patient review upon discharge to ensure continued care (Burden et al. 2005). The programme demonstrated the value of nurse-led care, which may be more relevant to long-term patient care (Bhattacharya et al. 2007).

As a final note on recommendations, patients’ clinical characteristics and lifestyle behavior need to be considered when prescribing insulin regimens. For example, beginning patients on fixed-dose insulin with automatic triggers works well for specific patient subgroups. Fixed-dose insulin could be disastrous for others who need a more individualised insulin regimen based on their clinical characteristics. A person who is severely hyperglycemic due to a known short-term time-limited event might need insulin to control glucose levels but this patient would need to be tracked and monitored so that the dose could be modified or insulin discontinued when the temporary clinical status was no longer influencing glucose levels (Hellman 2012).

Country case study: US

Kaiser Permanente’s Southern California Permanente Medical Group in the United States exemplifies a successful and targeted chronic disease management programme for diabetic patients to ensure timely medicine use.
A diabetes-focused disease management programme improved testing and identified undiagnosed patients

BACKGROUND

The Southern California Permanente Medical Group (SCPMG) delivers care for more than three million citizens of southern California; many of these have diabetes. Diabetes care has been traditionally fragmented with little coordination between GP, pharmacist, and specialist. SCPMG had developed guidelines for diabetes care including recommendations for physical exam, laboratory tests, and medications management, but compliance was sporadic.

INTERVENTIONS

Data collection within a web-based diabetes registry and tracking system was developed, linking pharmacies, laboratories, and providers.

A reminder/prompt system issued reminders to physicians (regarding patient’s progress) and patients (regarding overdue tests and appointments).

Protocol/procedure training for pharmacists was increased. It included patient counselling and, in the inpatient setting, certain treatments were triggered automatically in response to elevated blood sugar levels.

OUTCOMES

• **Testing levels increased**: Microalbuminuria testing increased from 10% to 55% and lipid testing increased from 44% to 65%.

• **Hospitalisations**: The system saw improvement in hospitalisation rates and a reduction in overall hospital days per 1000 members with diabetes between 1995 and 2000.

• **Identifying undetected at-risk patients**: Patients identified as having diabetes increased from 80,407 (1994) to 155,999 (2000), a 94% increase.

KEY CAPABILITIES

Clinical information systems/Health IT: Robust health IT enabled data collection and the series of reminders and prompts for patients, clinicians, and pharmacists.

Organisational buy-in: Dissemination of guidelines, education, and provider feedback are critical. Clinicians and pharmacists can override or otherwise ignore the system if they don’t understand or support its functions.

Source: Hyatt et al. 2002.
Background analysis

CONTEXT: DEFINING THE PROBLEM

The prevalence of diabetes is on the rise across the world, according to an estimate by the International Diabetes Federation 6.4% of the world’s adult population (285 million) are living with diabetes in 2010. This figure is expected to reach 7.8% by 2030, which would correspond to 438 million people. Currently, more than 70% of patients live in low- and middle-income countries. Diabetes can result in long-term complications if left untreated, including death in the most advanced cases. The most common complications are heart disease and stroke, blindness, high blood pressure, kidney failure, and damage to the nervous system.

Diabetes progresses as a life-long disease for which there is currently no cure. Late-stage patients also incur huge cost to the health system when symptoms and complications manifest. WHO estimates that the direct healthcare costs of diabetes-related illnesses range from 2.5% to 15% of a country’s annual healthcare budget (WHO 2012). Diabetes also greatly affects the quality of life of patients as the complications occur in multiple organ systems.

The severity of type 2 diabetes can be delayed through responsible medicine use in the early stages of the disease to manage glucose levels and inhibit the progress of diabetes and subsequent complications. While early management of type 2 diabetes necessitates regular monitoring and interventions with oral medications, IMS Health research focused on the use of insulin, an expensive treatment option that is often the last resort for patients as disease severity increases and oral medications no longer work. This analysis is a microcosm of a larger challenge with relation to timely medicine use.

The importance of timely provision of insulin for those who need it is illustrated in a 2011 study by IMS Health. This study used real world data analysis in Germany, France and the UK to demonstrate the impact of delayed insulin onset on macrovascular complications from 2005 to 2010 among type 2 diabetes patients. In 2005 and 2010, median duration until insulin initiation increased in all three countries, and this duration (measured in years) was accompanied by an increase in median HbA1c levels and mean number of diabetes-related complications per patient. Additionally, the percentage of patients with at least one macrovascular event and the mean number of events before insulin initiation was higher in 2010 compared with 2005 (Kostev 2011). Figures 9 and 10 demonstrate the results.

Similar results have been found in other studies, which also demonstrate the correlative relationship between HbA1c level trends and time to insulin initiation. Figure 11 demonstrates HbA1c level rise as preinsulin years increase, accommodated by a rise in oral medicine intake. The oral therapy escalation in this study was incrementally less effective and this may be for a number of reasons, including reduced adherence from polypharmacy and lack of additive effect of multiple oral combinations when endogenous insulin secretion is compromised (Evans et al. 2010).

**FIGURE 9: HBA1C OUTCOMES ARE WORSE WHEN TIME TO INSULINISATION FOR PATIENTS WHO SHOULD BE ON INSULIN INCREASES**

![Graph showing HbA1c outcomes](image-url)

*For subjects with a first time prescription of insulin (ATC:A10C) who started treatment in years 2005 and 2010.

Sources: IMS Institute for Healthcare Informatics, 2012; IMS Disease Analyser, 2005 and 2010.
There may be good reasons for such trends and variations between countries to exist. Barriers to early initiation of insulin therapy include patients’ and physicians’ misconceptions about the role of insulin for glycemic control. Among patients, there may be a phobia towards injections (despite most insulin injections being user-friendly through ‘pen needles’) or misconceptions about impact of insulin on complications such as blindness, renal failure, fear of hypoglycaemia, or early death. Physicians may not provide insulin due to inadequate resources or personal preferences (Coulter 2012).

**IMPACT ASSESSMENT**

Based on analysis and estimations from IMS Health on the likelihood of macrovascular events from patients who are not given insulin in a timely manner, countries can avoid significant costs from preventing macrovascular events. Germany, France, and the UK can potentially avoid 13%, 8% and 4% of diabetes expenditures from macrovascular events, respectively, by earlier insulin treatment for patients who have been identified as needing it. Figure 12 summarises these results.

Similar analyses by IMS Health demonstrated the impact of timely insulin interventions on outcomes. In the UK, initiating insulin increased life expectancy by 0.61 years vs. delaying initiation for eight years (Goodall et al. 2009). Regular monitoring of glucose levels can help determine the most appropriate treatment therapy and prevent costly and debilitating painful events such as stroke and myocardial infarctions.
FIGURE 12: UP TO 13% OF DIABETES SPENDING MAY BE AVOIDED WITH TIMELY TREATMENT


References


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* Prevalence figures may vary depending on the methodology and source used; These figures are from the International Diabetes Federation Atlas 2012; Other figures would change the cost avoided result.

** Extrapolated from the likelihood of patients on insulin with delayed insulinisation from IMS Disease Analyser data as average of figures in 2005 and 2011.

*** Based on average costs for treating stroke and myocardial infarction, most likely macrovascular events among type 2 diabetic patients.
References continued


Hellman, R. Personal communication with Richard Hellman, MD, Fellow in the American College of Physicians, Fellow of the American College of Endocrinology. Apr., 2012


References continued


Ortiz, D.D. 2006. Using a Simple Patient Registry to Improve Your Chronic Disease Care. *Family Practice Management*, 13, (4) 47


Teerawattananon, Y. Personal communication with Yot Teerawattananon, Health Intervention and Technology Assessment Programme, Thailand. Apr., 2012


References continued


Viral Hepatitis Prevention Board. The Clock is Running....1997: Deadline for Integrating Hepatitis B Vaccinations into all National Immunization Programmes, 1996. 1996. Fact Sheet VHPB/ 1996/1


IV. Medicine use revisited: Six primary levers of opportunity

3. RIGHT MEDICINE TO THE RIGHT PATIENT

Optimise antibiotic use

Antibiotic misuse and overuse contribute 11% of the world’s total avoidable cost due to suboptimal medicine use.
3. RIGHT MEDICINE TO THE RIGHT PATIENT: OPTIMISE ANTIBIOTIC USE

Antibiotic misuse and overuse contribute 11% of the world’s total avoidable cost due to suboptimal medicine use.

A total of 0.9% of global total health expenditure (THE), or 54bn USD worldwide, can be avoided from preventing antibiotic misuse or overuse.

There is wide variety among countries for this lever because many different factors contribute: healthcare infrastructure, elderly population, medicine intensity in the country, and affordability play the greatest roles. Brazil and China have been known for their recent policies to reduce antibiotic consumption, and therefore resistance. Countries such as Australia, the UK, the US and their peers tend to have challenges as well, due to easy access to low-cost antibiotics and limited regulation on their use.

Figure 13 below provides a snapshot summary of the relative avoidable costs out of THE. Data and respected ranges were estimated based on a combination of estimated and real values as well as data reliability. Where there are only two points, the point estimate is the minimum. Global average values are weighted by country total health expenditure.

FIGURE 13: AVOIDABLE COSTS (% OF THE) AT THE COUNTRY LEVEL

Source: IMS MIDAS, 2009 and 2011; World Bank 2009; WHO 2009; USD in 2011; Please see methodology section for details on global calculations which include 186 countries
Ministerial relevance and recommendations

- Antimicrobial resistance from antibiotic misuse/overuse is not news: this has been a public health threat for around a decade, primarily driven by supply-side factors such as over-prescribing.
- A multifaceted approach driven by Ministerial political leadership and capability support focused on informatics can reduce downstream costs in terms of hospitalisations and deaths.

## RECOMMENDATIONS: PRIORITISE NATIONAL-LEVEL SURVEILLANCE AND TRACKING, ENSURE GUIDELINE DEVELOPMENT AND COMPLIANCE, REALIGN PRESCRIBING AND DISPENSING INCENTIVES, LIMIT PRESCRIBING AUTHORITY AND INVEST IN DIAGNOSTIC TEST CAPABILITIES

<table>
<thead>
<tr>
<th>POTENTIAL MOH INTERVENTIONS</th>
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</tr>
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<tbody>
<tr>
<td>Prioritise good governance of antibiotic use at the national level by actively monitoring antibiotic use and tracking resistance</td>
<td>Sweden (Strama), USA (NARMS), France (ONERBA), EU funded (ESAC, ESAR, APREC)</td>
<td>Low cost</td>
<td>Medium - High</td>
<td>3-5 years</td>
</tr>
<tr>
<td>Develop national treatment guidelines and update them regularly based on antibiotic resistance trends</td>
<td>Australia, Finland, Sweden</td>
<td>Moderate cost</td>
<td>Medium - High</td>
<td>3-5 years</td>
</tr>
<tr>
<td>Develop patient education programmes and public campaigns</td>
<td>France, US</td>
<td>Moderate cost</td>
<td>Medium</td>
<td>0-2 years</td>
</tr>
<tr>
<td>Implement mandatory reporting of antibiotic use by provider</td>
<td>South Korea, Sweden, Brazil</td>
<td>Moderate cost</td>
<td>Medium</td>
<td>0-2 years</td>
</tr>
<tr>
<td>Limit/segment the authority to prescribe varied types of antibiotics by prescriber and/or dispenser type (e.g., highly valuable antibiotics for designated physicians, particularly in hospitals)</td>
<td>Thailand (approval programme), Turkey, Brazil</td>
<td>Low cost</td>
<td>Low - Medium</td>
<td>0-2 years</td>
</tr>
<tr>
<td>Train and educate health professionals on AMR from antibiotics in the work place and academic institutions</td>
<td>Netherlands, Sweden</td>
<td>Low cost</td>
<td>Medium</td>
<td>0-2 years</td>
</tr>
<tr>
<td>Invest in diagnostic testing capabilities to justify antibiotic use at point of care; learnings from rapid diagnostic testing in malaria may help</td>
<td>Netherlands</td>
<td>Moderate cost</td>
<td>High</td>
<td>3-5 years</td>
</tr>
</tbody>
</table>
Basis for recommendations: Interventions and policy options

Evidence shows that the implementation of both strategic and operational interventions is most effective in controlling antibiotic resistance (Fishman 2006). A specific example is from Thailand with the Antibiotics Smart Use Programme where a multifaceted approach including creating treatment guidelines and patient education (strategic interventions) alongside a surveillance system (operational) resulted in a substantial (18%-46%) reduction in antibiotic use (Sumpradit et al. 2011). A ranking of interventions is not possible since the combination will depend on specific health system circumstances.

These interventions should be considered alongside the strategies highlighted in the WHO’s Global Strategy for Containment of Antimicrobial Resistance (World Health Organization 2001).

STRATEGIC INTERVENTIONS

1. Prioritise good governance of antibiotic use at a national level.

Several countries have convened a specific national/transnational body made up of multiple stakeholders to address the issue of antibiotic resistance. For example:

- National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS) in the US.
- Canadian Integrated Program for Antimicrobial Resistance (CIPARS) in Canada.
- Observatoire National de Epidémiologie de la Résistance Bactérienne aux Antibiotiques (ONERBA) in France.
- The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) in Denmark.

Evidence from Malaysia shows that monitoring MRSA using WHONET to facilitate analysis of antimicrobial susceptibility test results resulted in decreased MRSA rates from 29.5% in 2003 to 22% in 2010 (World Health Organization 2012).

The European Union funds regional governance bodies to track the consumption of antibiotics and the status of resistance with a collaborative approach: European Surveillance of Antibiotic Consumption (ESAC); European Surveillance of Antibiotic Resistance (ESAR); Antibiotic Resistance and Prescribing in European Children (APREC).

This research also shows that these national bodies are multistakeholder, which is a reason for their added value and effectiveness. For example, NARMS in the US is a collaboration among the Centers for Disease Control and Prevention (CDC), US Food and Drug Administration (Center for Veterinary Medicine) and US Department of Agriculture (Agricultural Research Service). Furthermore, NARMS works in partnership with state and local health departments and their laboratories.

2. Develop national treatment guidelines and update them regularly based on evidence.

A study in Finland demonstrated that erythromycin resistance for streptococci decreased from 16.5% to 8.6% over a four-year period during a nationwide programme relying on national guidelines to limit the use of erythromycin (Colgan and Powers 2001). In Sweden, national recommendations for the treatment of various diagnoses common in general practice such as acute otitis media (ear infections), acute pharyngotonsillitis, impetigo, acute sinusitis, urinary tract infections, and lower respiratory tract infections are part of the national responsible use of antibiotics strategy.

Moreover, in Australia national guidelines on the treatment of most infections and on prophylaxis are frequently updated to guide antimicrobial use within both hospital and community settings. Australia has a lower use of fluoroquinolones when compared with other countries as well as lower levels of fluoroquinolones resistance (World Health Organization 2012).
Furthermore, guidelines should be enforced and made mandatory as they are in France. When guidelines are not followed consistently, providers face scrutiny from the clinical community (Le Pen 2012).

3. Develop patient education programmes and public campaigns.

It is important to educate patients in order to avoid a defensive reaction to physicians when an antibiotic is not prescribed and to inform patients that antibiotics are not always the appropriate treatment.

In France, a public campaign (‘Antibiotics are not automatic!’) has contributed to the reduced unnecessary over prescription of antibiotics (See the France case study).

In the US, a multifaceted education intervention (printed materials and pamphlets in waiting and examination rooms for patients) contributed to reduced antibiotic prescribing rates (Finkelstein et al. 2001).

OPERATIONAL INTERVENTIONS

4. Actively monitor antibiotic use and track resistance.

The antibiotic bodies noted above (NARMS, CIPARS, ONERBA, etc.) are also involved in active surveillance of antibiotic use and resistance.

Multinational collaborations as noted above have also been assembled to address the issue, such as ESAC, ESAR, and ARPEC.

5. Implement mandatory reporting of antibiotic use.

When the Ministry of Health of Indonesia required that every hospital implement an antimicrobial resistance control program and report their work yearly, the proper use of antimicrobials improved (Djanun et al. 2011). In South Korea, the government has reduced the use of antibiotics by implementing an effective national programme wherein the antibiotic prescribing rate (APR) for acute upper respiratory tract infection of healthcare providers is publicly disclosed on the website of the Health Insurance Review Agency in the form of report cards for each facility (Choi and Reich 2011).

In the Netherlands, a country with the lowest antibiotic prescribing in Europe, not only do prescribers report their own use but they also receive individual reports that compare their practice with expected guidelines and outcome standards. This is overseen by SWAB, The Dutch Working Party on Antibiotic Policy, an initiative of the Society of Infectious Diseases and the professional societies of medical microbiologists and hospital pharmacists. Central collection of information like this facilitates the use of specific interventions that can support reduced use among specific prescribers or improve understanding of why some prescribers may have higher than average use in their clinic.

6. Train and educate health professionals on antimicrobial resistance in the workplace and academic institutions.

A recent study from the University Medical Centre Utrecht, The Netherlands, emphasised the importance of physician education in improving rational use of antibiotics (van der Velden et al. 2011). However, a study of antibiotic prescriptions in primary care in the Netherlands shows that education based on guidelines is not enough to change prescription behaviour. Additional interventions must complement provider education including monitoring and detailed feedback, as described above (van der Velden et al. 2011).

Furthermore, evidence from the Netherlands also shows that training to enhance communication skills improves antibiotic utilisation. Providers who were able to communicate effectively with their patients (e.g., eliciting patient concerns, asking their view of antibiotics) were able to increase patient participation and manage patient demands and pressures (Cals et al. 2009).

Lastly, the use of up-to-date guidelines and recommendations in practice would provide providers with a ‘backbone’ to harmonise medical practice through evidence-based guidelines.

This field has much to learn from the successes of rapid diagnostic testing developments for malaria.
7. Invest in diagnostic capabilities at point of care.

Existing evidence suggests that the use of diagnostics decreases the overall volume of antibiotics prescribed, which has been linked to decreased resistance (Okeke et al. 2011). However, few countries have nationwide point-of-care diagnostic capabilities in place. Instead, many current diagnostic tools are archaic methods that are not timely (lag time between administering test and receiving results) and require laboratory resources and skills. The former limitation places a burden on the patient as there is a need for multiple visits to the provider. The latter restriction is a disadvantage for use in resource-limited settings.

This field has much to learn from the successes of rapid diagnostic testing developments for malaria. WHO guidelines currently recommend the use of diagnostics for all suspected cases of malaria in order to prevent the unnecessary use of antimalarials (World Health Organization 2010). Diagnostics for malaria include microscopy and rapid diagnostic tests. Limitations in the use of microscopy due to the lack of infrastructure and technical skills has established a market for rapid diagnostic testing. Studies have shown that the use of such rapid diagnostic tests for malaria has improved the overuse of antimalarial therapies in low-income settings (Hopkins et al. 2009). For instance, evidence from Madagascar suggests that between 2007 and 2008 rapid diagnostic tests were used in 93% of suspected malaria cases and malaria was confirmed in 10% of those cases, leading to a reduction of antimalarial prescriptions (Hopkins et al. 2009).

There are two rapid diagnostic tests to assess the need for antibiotics that are used in practice in different countries, though not on a consistent nation-wide level: Streptococcal antigen tests and C-reactive protein tests. Streptococcal antigen tests currently used in practice within the US, France, and Finland have been shown to be effective in terms of reducing unnecessary antibiotic prescribing (Okeke et al. 2011). The use of a rapid C-reactive protein test in Denmark demonstrated a cost savings of 111,160 USD per annum for a county with a population of 340,000. However, there was no difference in antibiotic prescriptions, and the savings were mainly based on the reduced use of laboratories as a result of the point-of-care testing (Dahlerr-Eriksen et al. 1999). Another study conducted in the Netherlands suggests that the introduction of C-reactive protein point-of-care testing reduced antibiotic prescriptions for lower respiratory tract infections. Specifically, physicians that used the C-reactive protein test prescribed antibiotics to 31% of patients compared with 53% of physicians who did not use the test (Cals et al. 2009).

Rapid diagnostic tests are not always cost saving, which is also a difficult metric to derive in this area. For example, although there can be reductions in spending on antimalarials (in many instances, these costs are partially or wholly subsidised), overall cost savings will depend on the cost of the test (which can range from 0.55-1.50 USD), malaria prevalence, and the cost of alternative treatment when malaria has been ruled out (Wongsrichanalai et al. 2003). A study in Tanzania showed that the introduction of rapid diagnostic tests in Dar es Salaam reduced per patient drug spending (0.36 USD and 0.43 USD for patient expenditure and providers costs, respectively) but these drug savings did not offset the cost of the tests (Yukich et al. 2010).

An analysis of total savings would depend on the type of antibiotics and duration of treatment avoided. In the Netherlands, antibiotic costs in a hospital can range from 0.80 EUR per dose for penicillin G to 35 EUR per dose for ceftriaxone. Furthermore, direct costs savings would include savings in material costs per dosage from needles, syringes, infusion fluids, etc. (Oosterheert et al. 2003).

There are three key barriers to current diagnostic test implementation for antibiotic use that can be overcome if Ministers incentivise their use and encourage investment in improving the technology. Firstly, clinical ambiguity over the accuracy and sensitivity of both the C-reactive and streptococcal antigen tests has inhibited their widespread use (Edmonson and Farwell 2005; van der Meer et al. 2005). Furthermore, the low cost of most antibiotics disincentivises physicians from using diagnostics as they are more inclined to save time and money through antibiotic administration (and do not consider resistance costs) (Edmonson and Farwell 2005; Okeke et al. 2011).
Finally, the C-reactive protein test, the latest rapid diagnostic tool, is significantly more expensive than most first-line antibiotics at between 12 to 80 USD depending on the commercial entity selling the diagnostic and the reimbursement scheme (Health Testing Centers.com 2012).

8. Create the right incentives for the correct use of antibiotics.

An intervention to disincentivise providers from overprescribing in China (with financial penalties) has contributed to the reduction of antibiotic use (See the China case study).

Recent pharmaceutical reform in Korea has eliminated provider’s profit from prescribing and dispensing medicines. Evidence shows that prior to the reform, Koreans consumed more drugs than any other developed country resulting in an increased level of antibiotic resistance due to the financial incentives for physicians and pharmacists to dispense more drugs (Health Testing Centers.com 2012; Kwon 2003).

9. Limit/segment the authority to prescribe varied types of antibiotics by prescriber type.

A study from Thailand showed that implementing an antibiotic approval programme improved antibiotic use (Thamlikitkul et al. 2011). Furthermore, a study from Turkey showed that restricting the use of expensive antibiotics and intravenous antibiotics (approval needed from an infectious disease specialist) showed clear benefits including an overall decrease of antibiotic use (approximately 50%) and an increase in appropriate antibiotic use. This resulted in a decrease in total expenditure of all antibiotics by 19%, accounting for a savings of 332,000 USD (Ozkurt et al. 2005).

Countries have also implemented interventions that have restricted the use of specialised antibiotics with the purpose of maintaining a ‘reserve’ for highly resistant patients in cases of major epidemic events. In France, for instance, hospital pharmacists have special guidelines from the Ministry of Health to do this in cases of public health emergency (Le Pen 2012).

Evidence shows that the implementation of both strategic and operational interventions are most effective in controlling antibiotic resistance (Fishman 2006). A specific example from Thailand with the Antibiotics Smart Use Programme where a multifaceted approach included creating treatment guidelines and patient education (strategic interventions) alongside a surveillance system (operational) resulted in a substantial reduction (18%-46%) in antibiotic use (Sumpradit et al. 2011).

These interventions should be considered alongside the strategies highlighted in the WHO’s Global Strategy for Containment of Antimicrobial Resistance (World Health Organization 2001).

Country case studies: Sweden, Brazil, China, France

Four country case studies that have implemented national policies successfully: Sweden, Brazil, China, and France. All are multifaceted.

Country case studies: Sweden, Brazil, China, France

Four country case studies that have implemented national policies successfully: Sweden, Brazil, China, and France. All are multifaceted.
The Swedish Strategic Programme Against Antibiotic Resistance (Strama) reduced use and improved outcomes

BACKGROUND

In the early 1990s, Swedish health officials became alarmed at the increasing use of antibiotics and the spread of penicillin-resistant pneumococcal clones. The overuse of antibiotics (both in human and animal use) has been linked to increased antibiotic resistance.

INTERVENTIONS

Surveillance included local groups that monitor antibiotic use and resistance. Data from local groups reported to the national level. Prescribers are provided with data on a local or individual basis (for comparison with other prescribers).

Educational activities and conferences for healthcare professionals are provided with regular and updated information about the Strama programme and antibiotic use in Sweden.

OUTCOMES

- The proportion of Streptococcus pneumonia with decreased sensitivity to penicillin V has stabilised (around 6%).
- Sweden is among the countries with the lowest rates of methicillin-resistant Staphylococcus aureus (MRSA) (<1%).
- Antibiotic use decreased from the mid-1990s without measurable negative consequences.

Investigative efforts have been initiated to understand the slight sales increase during 2004-2007. Causes may include high demand-side pressure due to the spread of vancomycin-resistant enterococci (VRE) over several countries and poor compliance to guidelines.

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Sources: Swedish Institute for Communicable Disease Control 2010; Struwe 2009.
**KEY CAPABILITIES**

**Multidisciplinary collaboration:** Regular dialogue with various stakeholders to inform decisions on treatment guidelines, national antibiotic targets, and thought leadership.

**Political will and commitment at both the local and national levels:** Resistance is reported for some pathogens according to the Communicable Disease Act but for most pathogens is performed voluntarily. Since 2011 all local Strama groups have a mandate and financial support in accordance with a governmental initiative on antimicrobial resistance. Critical success factors of the programme have been local engagement and the multidisciplinary approach.

*Sources: Molstad et al 2008; Cars 2012.*
Recent legislation in Brazil has reduced antibiotic overuse and misuse

BACKGROUND

Antibiotic overuse and abuse in Brazil has been driven by both supply-side and demand-side factors. In 2002, a survey found that around 74% of pharmacies in a medium-sized city in Brazil would sell antibiotics without a medical prescription. In the pharmacies that would sell antibiotics without a prescription, amoxicillin was the most indicated antibiotic. Research in São Paulo by the Special Laboratory of Clinical Microbiology (Unifesp) suggested that doctors were prescribing antibiotics in smaller doses than necessary, or antibiotics that were ineffective against respiratory disease pathogens such as pneumonia, pharyngitis, and sinusitis. Antibiotics are commonly self-medicated in Brazil.

INTERVENTIONS

The National Agency of Health Surveillance (ANVISA) put in place two pieces of legislation specifically targeting pharmacists to control antibiotic misuse and overuse. RDC 44/2010 (October 26th 2010) establishes that antibiotics cannot be sold without a prescription including: duplicate forms (one to be retained by the pharmacy); the name of the antibiotic, dosage, concentration, method of administration and quantity. RDC 20/2011 (May 5th 2011) expanded RDC 44/2010. It specifies coverage procedures in cases of prolonged use of the medication, and encourages pharmacist review on the number of drugs prescribed per prescription to alert for antibiotics. Both legislations make it more cumbersome to prescribe and dispense antibiotics since the administrative process is increased.
OUTCOMES

- Estimates of antibiotic consumption at the retail level are reduced 18% today compared to without legislation.
- This supports the aim of controlling patients’ antibiotic use.

AN ANTIBIOTIC FORECAST IN THE RETAIL SECTOR SHOWS THAT WITHOUT THE LEGISLATION, BRAZIL’S ANTIBIOTIC USE WOULD BE ABOUT 18% HIGHER

KEY CAPABILITIES

National leadership to collaborate with pharmacies: ANVISA received great support from key pharmacy associations in the health sector (e.g., Regional Council of Pharmacy of São Paulo, Federal Council of Pharmacy, Federal Council of Medicine, scientific societies of the health sector, etc.).

Surveillance on antibiotics dispensation: Essential to ensure that all pharmacies are complying with the legislation because the legislation indirectly encourages doctors to prescribe more consciously.

“‘If control on black label drugs (drugs that require a prescription and detailed reports) works, why wouldn’t it work with the red label ones (drugs that need a prescription but monitoring is not as stringent)?’” – Jaldo de Souza Santos, President, Federal Council of Pharmacy (2005).

Enforcement: A pharmacy that does not respect the legislation can be fined to up to $1.5Mn BRL and have their medications apprehended.


Recent reform in China has reduced antibiotic consumption by 15% over a six-month period

BACKGROUND

The average annual consumption of antibiotics per capita in China has been 10 times the level of consumption in the US. Among Chinese inpatients, 70% have received antibiotics, while the maximum percentage set by the World Health Organization is 30%. Perverse financial incentives have been prevalent. Doctors’ incomes are closely linked to prescription of certain pharmaceuticals, with potential for bonuses and kickbacks from hospitals and/or companies.

INTERVENTIONS

The National Antibiotic Restraining Policy (2012) includes limitations on the varieties of antibiotics granted to hospitals based on grade and function. It capped user ratios (share of antibiotics among all prescription drugs) and implemented penalties if doctors are found using antibiotics inappropriately (e.g., warnings, suspensions, withdrawal of license).

Regional initiatives help monitor national policy implementation. For example, Beijing implemented an ongoing health bureau survey of antibiotic usage at 165 city hospitals (with risk of downgrading for those who overuse antibiotics). A similar scheme is rolling out in Shanghai.
Since implementation of the policy, antibiotic use in hospitals reduced by 15% over a six month period.

**ANTIBIOTIC CONSUMPTION DECREASED BY OVER 15% SINCE THE NATIONAL POLICY WAS RELEASED**

<table>
<thead>
<tr>
<th>MAT Growth Rate (%)</th>
<th>National market excluding antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>Systematic antibiotics (J01ATC)</td>
</tr>
<tr>
<td>30</td>
<td></td>
</tr>
<tr>
<td>25</td>
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<td>20</td>
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<td></td>
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<tr>
<td>5</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
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<tr>
<td>-5</td>
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</table>

Annual growth rate trend of antibiotics vs. national market (annual growth over previous year)

Sources: IMS Hospital Audit, 2011; IMS Institute for Healthcare Informatics, 2012.

**KEY CAPABILITIES**

**Surveillance:** Continuous monitoring of antibiotic usage is required to demonstrate the long-term impact of the restriction policy. The Chinese government has shown commitment to national surveillance capabilities through surveys and electronic health records (EHRs) in some hospitals where available (e.g., Shanghai).

**Enforcement:** New legislation such as this must be extensively enforced, especially as regulations may be interpreted differently provincially. China’s case demonstrates that penalties such as license withdrawal and cancellation of prescription-writing privileges may be necessary to change behaviour.

**Patient education:** Studies on this policy have shown that patients who displayed some knowledge of antibiotics were far less likely to be prescribed the drugs by their physicians. This suggests that patients are also accountable for behaviour that has driven antibiotic overuse. Targeting patients as well as physicians with information may be critical.

*Sources: Global Times 2011; China Daily 2011; China Daily 2012a; China Daily 2012b; Ma 2012; Baidu 2011.*
IV. MEDICINE USE REVISITED: SIX PRIMARY LEVERS

OPTIMISE ANTIBIOTIC USE: CASE STUDY 10 – FRANCE

National plans for preserving antibiotic effectiveness resulted in a 16% reduction in consumption

BACKGROUND

With more than 100 million prescriptions per year in 2001, France has had the greatest antibiotic prescription rate per capita among developed countries. Surveys showed that about 30% of the prescriptions in outpatient care were inappropriate because of the viral nature the infection and the lack of risk factors for complications. Overprescription has led to a risk of development of bacterial resistance in the context of scarcity of drug innovation.

INTERVENTIONS

Three national plans “for preserving the effectiveness of antibiotics” were launched by the French National Health Insurance agency successively covering the periods 2001-2005 (1st plan), 2007-2010 (2nd plan), and 2011-2016 (3rd plan). The initial interventions were: improvement of public awareness about the risk of overconsumption (“antibiotics are not automatic”); promotion of diagnostic tools for professionals (quick tests); improvement of antibiotic use in hospitals (creation of a specific pharmacy and therapeutics committee for antibiotics, diffusion of guidelines, etc.); creation of an observatory of antibiotic consumption and bacterial resistance. The budget for the 1st and 2nd plans is estimated at 7.5Mn EUR per year (of which 5.5Mn EUR is dedicated to the public campaign).

OUTCOMES

- Between 2001 and 2004 antibiotic consumption declined by 16%, especially among children (-26% in age 0-6 years). This corresponded to an annual reduction of 6.4 million inappropriate prescriptions and a 100Mn EUR yearly financial savings to the health system.

- At the same time, the frequency of pneumococci with a reduced sensitivity to penicillin showed a marked improvement.

Sources: HCSP 2010; IMS Institute for Healthcare Informatics, 2012.
OUTCOMES continued

- Nevertheless, consumption reached a plateau from 2005 to 2010, with a slight increase since 2009.
- A 3rd plan (2011-2016) was deemed necessary, with a reduced number of objectives and an improvement of follow-up tools.

**KEY CAPABILITIES**

This intervention initially worked because of the engagement of all the stakeholders, especially doctors and patients, through the public campaigns. The plan had a public health priority rather than economic objectives. However, over time the effects of the public campaigns have shown to be less impactful, which indicates the need for a multifaceted, sustained effort rather than a primary initiative.

Sources: HCSP 2010; Le Pen 2012.

### REDUCTION IN ANTIBIOTIC CONSUMPTION IN FRANCE

[Graph showing the reduction in antibiotic consumption in France from 1998 to 2009, with defined daily doses (DDD) per 1,000 inhabitants.]

Sources: IMS Hospital Audit, 2011; IMS Institute for Healthcare Informatics, 2012.
Background analysis

CONTEXT: DEFINING THE PROBLEM

Over several decades and to varying degrees, bacteria causing common infections have developed resistance to each new antibiotic (World Health Organization 2012). Global antibiotic abuse (overuse and misuse) plays an important role in antimicrobial resistance (AMR) and is a global threat against public health (Straand et al. 2008). Indeed, the issue of antibiotic resistance has been a priority area for the World Health Organization (WHO) as an international call for action has been repeatedly expressed: In 2001, the Global Strategy for Containment of Antimicrobial Resistance, 2004 Priority Medicines for Europe and the World Project: A Public Health Approach to Innovation and most recently in 2007, the World Health Report (Kaplan and Laing 2004; World Health Organization 2001; World Health Organization 2007).

Evidence suggests that antibiotic abuse is largely a supply-side phenomenon and that prescribing and dispensing behaviours should become a priority area of focus to control antibiotic resistance (Currie et al. 2011; Saver 2008). In some cases (e.g., in Brazil), antibiotic abuse also has been driven by patients who prefer using cheap antibiotics to treat acute diseases, and pharmacists easily provide them without control (See the Brazil case study).

While there is a wide range of antibiotics currently available on the market, research has shown that there are several antibiotics that are prone to misuse and overuse. In Sweden, the Swedish Strategic Programme Against Antibiotic Resistance (Strama) is continuously monitoring antibiotic use by comparing prescription patterns and trends within Sweden as well as among groups of prescribers. These antibiotics are often misused to treat illnesses that are common in general practice such as respiratory infections (e.g., sinus infection, some throat infections, some ear infections, most common colds and bronchitis) and urinary tract infections (Centers for Disease Control 2012).

Overuse and misuse of antibiotics occur in both the primary care setting and the hospital setting. Although overuse, misuse, and resistance were once predominately an issue in hospital settings, they are growing concerns in community/primary care settings, as well as in long term-care settings (Alanis 2005; Centers for Disease Control 2012; Weller and Jamieson 2004). Studies indicate that nearly 50% of antimicrobial use in hospitals is unnecessary or inappropriate (Fishman 2006). A study of antibiotic misuse in medium-sized Swiss hospitals showed that a high proportion of hospitalised patients received antibiotics (25%) of which 47% were categorised as antibiotic misuse, defined in the study as an absence of an indication for such antibiotics (Bugnon-Reber et al. 2004).

There are two main reasons for the misuse and overuse of antibiotics in both primary and secondary care settings from a supply-side perspective. These include misdiagnosis as well as perverse incentives.

Misdiagnosis

MISDIAGNOSIS LEADS TO THE OVERUSE OF ANTIBIOTICS

In many cases, overuse of antibiotics is prevalent when prescribed for viral infections, against which they have no effect (European Centre for Disease Prevention and Control). A US study showed that approximately 75% of ambulatory antibiotic prescriptions are for the treatment of five specific acute respiratory infections (otitis media, sinusitis, pharyngitis including tonsillitis, bronchitis, upper respiratory infections). However, these antibiotic prescriptions are unnecessary since these conditions are predominately viral (Gonzales et al. 2001). Several studies have demonstrated that acute otitis media in children can be managed without antibiotics (Siegel et al. 2003).

Furthermore, overprescription of antibiotics also occurs because of physician belief. For example, prophylactic antibiotics are overused due to the perception among many prescribers that their potency can prevent disease severity.
Antibiotic overuse is also common in surgical use. A Swiss study has shown that surgeons are particularly prone to keeping surgical patients on antibiotics for unnecessary long periods of time (Bugnon-Reber et al. 2004). The one-day prevalence study showed a quarter of inpatients on antibiotics, of which 47% was inappropriate and 28% lacked any indication for antibiotic use. Similar evidence has been found in hospitals in Iran (98% inappropriate use) and India (Gaash 2008).

**MISDIAGNOSIS LEADING TO MISUSE OF ANTIBIOTICS – THE BROAD-SPECTRUM STORY**

Misdiagnosis also occurs when the microorganisms that cause infections are not known, resulting in the prescription of broad-spectrum antibiotics, i.e. antibiotics that kill a large proportion of various bacteria and not only the bacteria responsible for the disease. Evidence from different parts of the world demonstrates the challenge when physicians use antibiotics as a panacea for different ailments. In a study of antibiotic use within the US outpatient setting between 1991-1999, findings show that physicians are increasingly turning to expensive (because of less generic competition), broad-spectrum agents, even when there is little clinical rationale for their use. Broad-spectrum antibiotics made up 50% of all antibiotic prescriptions for adults and 40% of prescriptions for children (Steinman et al. 2003). Evidence from Korea, Japan, and Turkey has shown that eliminating the overuse and misuse of broad-spectrum antibiotics may be the best solution in the control of resistant bacteria development (Livermore 2002).

Misdiagnosis that leads to the overuse and misuse of antibiotics can be the result of multiple, nonmutually-exclusive factors. The majority are supply-side such as lack of knowledge or training, prescriber beliefs (e.g., ‘newer is better’), lack of treatment guidelines (or inappropriate treatment guidelines), lack of technology to support prescription processes, and lack of diagnostics. Other factors are demand-side driven. For example, parents often demand antibiotics for children. A US study showed that doctors prescribe antibiotics 62% of the time if they perceive parents expect them and 7% of the time if they feel parents do not expect them (Centers for Disease Control, 2012). Other demand-side conditions include race, ability to pay, clinical pressures (e.g., address long waiting times by treating patients quickly with an antibiotic to meet their expectations), litigation concerns, etc. (Bugnon-Reber et al. 2004; Steinman et al. 2003).

**Perverse incentives**

From a prescription perspective, prescriber and pharmacy remuneration policies may result in the overuse and misuse of antibiotics. This has been particularly prevalent in China, which has the world’s most rapid growth of resistance (22% average growth in one study from 1994 to 2000) (Zhang and Harvey 2006). A recent study on the irrational use of medicines in rural China showed that prescription practices of rural healthcare providers and economic incentives from selling medicines are the main reasons for the high antibiotic utilisation (Sun et al. 2011). In Shanghai, evidence revealed that inadequate compensation mechanisms cause hospitals to rely heavily on the 15% to 20% drug price mark-ups. This refers to all drugs, but antibiotics account for almost 50% of these, resulting in overuse and irrational use of medicines in hospitals (Hu et al. 2001; Jiang 2012). As a common occurrence, antibiotics in China are often misused. For example, they are used to treat viral diseases or are inappropriately overused. This has led to the routine use of third-generation antibiotics.

Figure 14 on the following page, exemplifies the correlation between outpatient use of penicillins and the resulting antimicrobial resistance. Although this trend is well known, it is complex. According to the recent WHO Global Strategy report in 2012, “the relative contribution of mode of use—dose, duration of therapy, route of administration—as opposed to total consumption is poorly understood.”

Although the focus of this section is on overuse and misuse, it is worth noting that underuse of antibiotics may be a risk in some countries, especially in low-income regions where access may not be readily available.
The benefits of addressing antimicrobial resistance are multifold from a cost avoidance and health outcome perspective. Firstly, there are cost savings that could be realised if the overuse of antibiotics is addressed. For example, research shows that in the US it is estimated that antibiotics were prescribed 68% of the time during acute respiratory tract infection visits, and of those 80% were unnecessary according to CDC guidelines. The estimated cost of the misuse of antibiotics for adult upper respiratory infections is 1.1Bn USD per year (Center for Disease Control 2012).

Additionally, there are cost implications when antibiotics fail to work because the bacteria develop resistance. These implications include: longer-lasting illnesses, more doctor visits, extended length of stay, and the need for more expensive complex treatments (Alanis 2005).

Based on US studies of infection cost caused by antibiotic-resistant pathogens vs. antibiotic-susceptible pathogens, the annual cost to the US health care system of antibiotic-resistant infections is 21Bn to 34Bn USD and more than eight million additional hospital days (Spellberg et al. 2011).

**FIGURE 14: OCCURRENCE OF STREPTOCOCCUS PNEUMONIAE AGAINST OUTPATIENT USE OF PENICILLINS IN 17 EUROPEAN COUNTRIES**

**FIGURE 15: COST OF ANTIBIOTIC OVERUSE AND RESISTANCE IN THE US**

*Societal costs of antibiotic-resistant infections: Treatment costs include hospital costs such as: length of stay, laboratory services, specialty consultations, bedside procedures, treatments and operation / management support and societal costs includes mortality and loss of productivity.


Similar or worse results come from other countries. An additional potential benefit in the control of antibiotic resistance includes a reduced need for research and development in new and relatively more expensive antibiotic medicines. The need for new antibiotics historically arose due to increasing resistance to older medicines. In the last 10 years, the pharmaceutical industry has been reluctant to invest in research and development of antibiotics (in 2004, only 1.6% of drugs in development by the world’s 15 largest drug companies were antibiotics) because of multiple factors including high costs, low returns, and a large generics market (specifically, narrow-spectrum antibiotics) (Morel and Mossialos 2010). Nevertheless, the demand for new antibiotics has been growing with the increasing challenge of resistance to existing medicines. Better use of existing medicines would reduce that demand and cost burden, since new medicines are expensive.

Finally, controlling resistant infections can improve mortality rates for a country (Cosgrove 2006; Morel and Mossialos 2010; Steinman et al. 2003). In the US, a 2007 study suggests that there are 18,000 deaths per year as a result of MRSA (Morel and Mossialos 2010). Furthermore, in the EU alone, it is estimated that infections with resistant bacteria causes around 25,000 deaths per year (Morel and Mossialos 2010).

3. OPTIMISE ANTIBIOTIC USE

References


Cars, O. Personal communication with Otto Cars, Swedish Institute for Communicable Disease Control, Sweden. Apr., 2012


Cosgrove, S.E. 2006. The relationship between antimicrobial resistance and patient outcomes: Mortality, length of hospital stay, and health care costs. Clinical Infectious Diseases, 42, (Supplement 2) S82-S89


Fishman, N. 2006. Antimicrobial stewardship. The American Journal of Medicine, 119, (6) 53-61


Le Pen, C. Personal communication with Claude Le Pen. May 3, 2012


Thamlikitkul, V., Rattanaumpawan, P., and Sutha, P. 2011. Randomized controlled study of antibiotic approval program on patients' clinical outcomes and antibiotic expenditures. *International Conference for Improving Use of Medicines*, #291


References continued


IV. Medicine use revisited: Six primary levers of opportunity

4. RIGHT MEDICINE TO THE RIGHT PATIENT
Prevent medication errors

Medication errors contribute 9% of the world’s total avoidable cost due to suboptimal medicine use
4. RIGHT MEDICINE TO THE RIGHT PATIENT: PREVENT MEDICATION ERRORS

Medication errors contribute 9% of the world’s total avoidable cost due to suboptimal medicine use.

A total of 0.7% of global total health expenditure (THE), or 42bn USD worldwide, can be avoided if medication errors are prevented.

Medication errors include those from prescribing, preparing/dispensing, administration and monitoring of medicines by healthcare professionals. Administration and prescribing are the larger components of overall avoided costs.

The most impactful factor driving variation between countries is medicine intensity: the amount of medicines in a country on average on a per capita basis as well as the amount of new chemical entities in a country. New medicine access is accompanied by a learning curve for their usage, which may result in errors. Healthcare infrastructure plays a role since there are simply more hands that transfer medicines across different stakeholders. This explains the imbalance towards higher-income countries in the chart below.

Figure 16 below provides a snapshot summary of the relative avoidable costs out of THE. Data and respected ranges were estimated based on a combination of estimated and real values as well as data reliability. Where there are only two points, the point estimate is the minimum. Global average values are weighted by country total health expenditure.

![Figure 16: Avoidable Costs (% of THE) at the Country Level](chart)

Source: IMS MIDAS, 2009 and 2011; World Bank 2009; WHO 2009; USD in 2011; Please see methodology section for details on global calculations which include 186 countries.
Ministerial relevance and recommendations

- In countries such as the US, ~25% of medication errors are preventable. Administration is consistently the highest driver of these errors, followed by prescribing.
- Medication errors are commonly identified and tracked in the hospital setting, though fears of penalty and a blame culture prevent healthcare professionals from discussing (and then addressing) this challenge.
- Ministers of Health can invest in informatics efforts to support clinical decision making. This may take time, and certainly investment, but benefits in terms of outcomes and costs avoided would be worthwhile.

### Basis for recommendations: Interventions and policy options

- Many interventions do not fall neatly into one error-prone process of medication errors. Computerised Physician Order Entry (CPOE) systems and Clinical Decision Support (CDS) systems affect a number of different error-prone processes to reduce medication errors and in some cases to address other areas (e.g., polypharmacy management, generic prescribing).

### RECOMMENDATIONS INCLUDE TECHNOLOGICAL TOOLS AND CULTURAL CHANGES TO REDUCE MEDICATION ERRORS AND IMPROVE OUTCOMES

<table>
<thead>
<tr>
<th>POTENTIAL MOH INTERVENTIONS</th>
<th>REFERENCE POINT</th>
<th>SPEND</th>
<th>HEALTH OUTCOME</th>
<th>TIME SCALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invest in health information technology infrastructure</td>
<td>Increase investments in e-prescribing</td>
<td>Sweden (E-health)</td>
<td>High cost</td>
<td>High</td>
</tr>
<tr>
<td>Invest in computerised Physician Order Entry</td>
<td>US (Norman Regional Hospital System using Zynx Health)</td>
<td>High cost</td>
<td>High</td>
<td>3-5 years</td>
</tr>
<tr>
<td>Implement barcoding systems in inpatient settings</td>
<td>The US Department of Veterans Affairs (VA) hospitals</td>
<td>High cost</td>
<td>High</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Implement a medication error reporting system</td>
<td>UK (National Patient Safety Agency)</td>
<td>High cost</td>
<td>Medium</td>
<td>3-5 years</td>
</tr>
<tr>
<td>Destigmatise error reporting</td>
<td>Support education efforts in hospitals</td>
<td>Low cost</td>
<td>Low</td>
<td>0-2 years</td>
</tr>
<tr>
<td></td>
<td>Identify and support local champions/opinion leaders’ in hospital</td>
<td>Low cost</td>
<td>Low</td>
<td>0-2 years</td>
</tr>
<tr>
<td></td>
<td>Encourage reduction of punitive measures against providers who commit errors</td>
<td>Low cost</td>
<td>Low</td>
<td>0-2 years</td>
</tr>
</tbody>
</table>
• Though this analysis presents health IT systems as separate entities, most often health system managers will choose to implement a comprehensive health IT infrastructure that includes some mix of e-prescribing, EHRs, barcoding, and CPOE/CDS.

• Changes to health IT systems are a primary solution to reducing medication errors because of the emphasis on interventions that can be taken at the national level. However, much of the problem with health IT lies in the process of implementation. Health system managers and hospital administrators frequently encounter resistance from physicians in adopting various health IT measures. Therefore, national-level policymakers can encourage IT intervention uptake through some of the ‘softer’ interventions to empower a culture that embraces medication error reporting.

• Interventions at the local hospital level should not be overlooked. For example, interventions to reduce the number of tasks given to each nurse have been shown to reduce the number of errors during medication administration. These suggest the importance of demonstrating a national commitment to local interventions.

Investments in health information technology (Health IT), a culture of reporting and research on workflow processes focusing on key behavioural sources of errors

Investments in health information technology (Health IT):

• CPOE: CPOE is a system of electronic entry where medical practitioners enter instructions for treatment of patients, most often in hospital settings. CPOE is intended to reduce medication errors through problems with handwriting and transcription, provide error checking for duplicative or otherwise incorrect doses and tests, and provide additional clinical decision support. A seminal study in 1998 found that CPOE was able to reduce the overall inpatient medication error rate by 83% (Bates et al. 1998). In Sweden, CPOE was implemented with a nation-wide electronic medical record system. At least half of GPs in Sweden have adopted this system with the purpose of improving overall patient care (Gartner 2009).

• CDS: CDS is an interactive system that uses various inputs of patient data to help guide a physician in making decisions surrounding the patient’s care (now being coupled with CPOE systems). Strong evidence from meta-analyses demonstrates that clinical decision support systems can both improve the quality of care and reduce medication errors (Kaushal et al. 2003; Kawamoto et al. 2005). Evidence from clinical decision support systems for renal insufficiency (which affects hundreds of medicines) suggests that CDS can reduce error rates. In one highly influential study, those in the control group were given the correct dose only 54% of the time, but those with CDS were given the correct dose 67% of the time. Financial analyses also proved that this is one of the most cost-effective interventions available (Bates et al. 2003; Kuperman et al. 2007).

Risks associated with CPOE: In a limited number of trials, CPOE has been shown to increase medication errors, suggesting that the conditions under which CPOE is implemented are essential to its success. (Han et al. 2005; Koppel et al. 2005). As the US Institute of Medicine (IOM) report states, “Avoiding these problems [errors associated with CPOE] requires addressing business and cultural issues before such strategies are implemented and aggressively solving technological problems during the implementation process.” Efforts and successes have been seen in fragmented health systems. For example, in the US, the Norman Regional Hospital System in Oklahoma used Zynx CPOE systems, which improved clinical process efficiency and therefore patient safety and quality of care (Zynxhealth.com).

• Electronic prescribing (e-prescribing): E-prescribing is a system of electronically generating and filling patient prescriptions in both inpatient and (though less commonly) outpatient settings. E-prescribing is intended to reduce errors associated with handwritten scripts. The largest source of transcription errors in the process comes from handwritten scripts that are not legible (Dean et al. 2002; Lesar et al. 1997). There is strong evidence that when implemented effectively, e-prescribing can prevent a large percentage of medication errors (meta-analyses cite variation in the error prevention rate between 30% and 84%) (Ammenwerth et al. 2008).
In Sweden, e-prescribing through a nation-wide e-health program has existed since 1983 as the world's first electronically transferred prescription system for outpatients. The system has been gradually rolling out across different counties since the 1990s, replacing paper medical records. The programme, which relied on collaboration between a nationwide pharmacy corporation, hospitals and primary health centers, has led to improved patient safety, efficiency gains from time-savings and modest financial savings. More than 70% of prescriptions are sent in electronic form from the physician's to dispense in any pharmacy in Sweden (Hellström et al. 2009).

The Kronoberg County in Sweden offers helpful lessons learned when it comes to deploying a comprehensive e-prescribing and e-health roll-out. While plans began in 1999, clinical implementation did not start until 2003 and net benefits were realized by 2006. The region took a long-term view of rolling out the programme and implemented the system only when the appropriate technology became available. The region's experience demonstrates the importance of management commitment across all levels, early implementation of least disruptive parts of the system and mitigation of organizational risks as key success factors to an effective e-prescribing and e-health programme (Dobrev et al. 2010). Recent evidence from a nation-wide patient attitude survey on the e-prescribing system supports the country's success in this area: 79% of patients regard e-prescriptions to be safe though the research also identified a need for more information about existing services (Hammar et al. 2011).

**Barcoding to minimise dispensing errors:** Barcoding matches the type of medication that is prescribed to the patient to a barcode that is attached to that patient. The nurse or physician validates and administers the medication after matching the barcode on the medication with the barcode on the patient. One trial showed that after bar code implementation, dispensing error rate fell by 31% and the potential adverse event rate fell by 63% (including so-called “near-misses”). When errors were broken down by type/variety, there was a 58% reduction in wrong medication errors, a 53% reduction in wrong dose errors, and total elimination of wrong dosage form errors (Poon et al. 2006). The US Department of Veterans Affairs (VA) already uses bar codes nationwide in its hospitals (US Food and Drug Administration 2011).

Even in the presence of relatively robust reporting technology, providers at the UK National Health Service (NHS) still underreport medication errors. A report from the NHS notes: “There are still very low numbers of medication incidents being reported by any primary care, mental health and some acute care organisations… Only a third of reports had the medicine name data field completed. Failure to use the voluntary medication name data field makes identifying the medicines most frequently associated with patient safety incidents difficult locally and nationally” (National Patient Safety Agency 2007 pp.14-15).

This highlights the need to have reporting software that is user-friendly. The UK National Patient Safety Agency (NPSA) rolled out an effective electronic reporting system for patient safety incidents in primary and secondary care and the independent sector in England and Wales.

**Create a culture of reporting:** This is essential for the future of medication error prevention. A survey of international medication safety experts found that “fear of consequences,” “a culture of blame in healthcare,” and “a need for organisational leadership and support” were three of the top five reasons for underreporting. This suggests that government officials and hospital leaders/administrators should work to destigmatise error reporting and perhaps develop a nonpunitive approach to error reporting (Terzibanjan 2007).

Additional studies find that the primary reasons individuals do not report errors are time pressure, fear of punishment, and lack of perceived benefit (Cohen 2000; Gallagher et al. 2003; Leape 2002; Uribe et al. 2002). Among physicians, the most commonly cited reasons are shame and fear of liability, loss of reputation, and peer disapproval (Gallagher et al. 2003; McArdle et al. 2003).

Reporting and ex-post analysis of errors facilitates future error prevention in several ways (Gallagher et al. 2003; Leape 2002; Rosenthal et al. 2001):

- Alerts about new medicines and associated hazards can be generated.
- Information gleaned from an individual hospital’s new methods or interventions can be widely disseminated.
• Accumulation of data from multiple hospitals and interventions can more easily lead to the development of guidelines or best practices.

There is strong evidence from a range of nonpunitive systems that voluntary reporting and fostering a culture of openness and destigmatisation surrounding errors are critical to increasing overall reporting rates in inpatient settings (Cohen 2000; Kohn et al. 2000). One strategy that has experienced success is for hospitals to adopt a formal policy of total disclosure of errors to patients. Of course, changes at the hospital level must be accompanied by corresponding changes in liability laws. But even in a strict liability environment, studies have found that hospitals that have a formal policy of disclosure and actively encourage physicians to disclose medication errors to patients have much higher levels of reporting and (perhaps unexpectedly) lower rates of malpractice litigation (Gallagher et al. 2007; Kachalia et al. 2003; Kachalia et al. 2010).

The National Patient Safety Agency (NPSA) in the UK has improving the way it has been tracking and reporting medication errors since January 2005. The NPSA leverages the National Reporting and Learning System, the world’s most comprehensive

### FIGURE 17: HEALTH IT INTERVENTIONS THAT CAN REDUCE MEDICATION ERRORS AMONG PROVIDERS AND PHARMACISTS

<table>
<thead>
<tr>
<th>Process</th>
<th>Stakeholder</th>
<th>Health IT Interventions</th>
<th>Capabilities</th>
<th>Error likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribing</td>
<td>Clinicians</td>
<td>Computerised Decision Support systems (CDS) / Computerised Prescriber Order systems (CPOE)</td>
<td>Guidelines</td>
<td>~5%</td>
</tr>
<tr>
<td>Transcribing</td>
<td>Nurses</td>
<td></td>
<td></td>
<td>15-25%</td>
</tr>
<tr>
<td>Dispensing</td>
<td>Pharmacists</td>
<td>E-prescribing</td>
<td>Culture</td>
<td>&gt;25%</td>
</tr>
<tr>
<td>Administration</td>
<td>Clinicians</td>
<td>Bar-coding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring</td>
<td>Nurses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinicians</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharmacists</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

database of patient safety information, to tackle patient safety challenges, including medication errors. The agency has seen a year-on-year increase in the reporting of medication incidents, including errors from medicines, the second largest group after treatment errors from October 2010 to September 2011 (NHS 2012). Encouraging reporting through activities which support clinicians and pharmacists in reducing medication errors have contributed to these results. A number of hospitals and primary care trusts (PCTs) in the UK have implemented policies for managing and supporting staff following a medication error. These are typically reviewed every two years and examples can be found in NHS Worcestershire PCT, NHS Peterborough Community Services, NHS University Hospitals of Leicester Trust and NHS West Essex Community Health Services (NHSa 2012; NHSb 2012; NHSc, NHSd 2012). Clear guidelines are in place to reduce medication errors and manage staff accordingly when they happen, including a ‘no blame’ culture. This is heralded at the national level as well by policy guidance from the Department of Health which specifies clinical governance in error reporting (UK Department of Health 2007).

Research on workflow processes focusing on key behavioural sources of errors: Poor processes, not error-prone people, are the main cause of medication errors (Chaiken and Holmquest 2002). Intuitively, the more steps there are in the health system, the more likely that medication errors occur. A study found that nurses averaged more than 15 minutes on each medication pass and they were at risk of an interruption or distraction with every medication pass (Elganzouri et al. 2009). Healthcare professionals face system challenges during the medication administration process that result in risks to patient safety. Therefore, it is necessary to conduct research on workflow, modify clinical behaviours, and develop more robust systems that reduce the probability of errors and adverse events.

There is some evidence that many physicians and providers simply do not understand how to report medication errors because of the growing complexity of the error documenting systems. Studies have shown that training sessions conducted by the government and/or hospitals can serve to train providers in the details of error reporting while simultaneously reducing the stigma associated with reporting (Miller et al. 2006; Uribe et al. 2002). An Egyptian study found that before training only 35% to 40% of health professionals were aware of how to report medication errors. Following training more than 90% believed error reporting benefits the health system (El Said et al. 2011).

In 2009, the US passed the Health Information Technology for Economic and Clinical Health (HITECH) Act to enable a nationwide, interoperable, private, and secure electronic health information system, including e-prescribing, which was a key effort to improve the performance of the US health system (Blumenthal 2010).

Figure 17 illustrates the range of health IT interventions that can be implemented to reduce medication errors across the medicine-patient provision process.

The design of such systems is not easy or straightforward. Central hubs that facilitate the kinds of interventions in Figure 17 can help. For example, in Stockholm a pharmacotherapy centre (PTC) has developed a range of e-based interventions to support clinical practitioners with e-prescriptions, a list of recommended medicines based on guidelines, a noncommercial website with drug information, an electronic decision-support system integrated into medical records, and knowledge databases on medicines and interactions. Dissemination efforts to obtain buy-in for use among physicians through drug therapeutic committees were crucial for this effort (Kardakis et al. 2011).

Country case studies: US, Australia, Oman

Three country case studies show successful implementation of systems that range from complex to simple to address medication errors: US, Australia, and Oman.
Targeted HIV-alert interventions in the order entry system reduced errors in hospital by 57% in the US

**BACKGROUND**

Clinicians treating HIV-affected patients at the University of North Carolina found a high rate of ARV-related errors in their hospital. In 72% of patients, at least one error was reported when the regimen was ordered, and in 56% of those patients, the error had the potential to cause clinical harm. Of the 82 identified errors, 45% were attributed to prescribing, 33% to dispensing, and 22% to documentation problems. Most errors involved administration of a drug with an adverse interaction with the ARV regimen.

**INTERVENTIONS**

A pocket-sized card was distributed to physicians, nurses, and pharmacists that provided doses, frequencies, and dosage forms of all ARV medications. Alerts were added to the pharmacy’s order entry system to notify pharmacists of adverse drug interactions. The prescriber order entry system was updated to include the most common dosing regimen as its default. Clinical pharmacists began reviewing all new regimens for interactions with the patient’s other existing prescriptions. All commercially available combination ARV agents were added to the hospital formulary.

**OUTCOMES**

- The percentage of patients in which at least one ARV medication error occurred on initial admission decreased from 72% to 15% (p<.001).
- At least one error occurred during hospitalisation in just 22% of the intervention patients but in 84% of the control patients.
- At least one class 2 or 3 error occurred during hospitalisation in 22% of the intervention patients and 65% of the control patients (p<0.001).
- The total number of errors in the intervention group was 86% less than in control group.

The University of North Carolina Hospital is currently working on several other pilot projects focusing specifically on transitions of care in other types of patients within the hospital. The goal is to have more pharmacist involvement in the medication reconciliation processes and in the discharge medication counselling processes in order to prevent and resolve errors associated with transitions of care.
OUTCOMES continued

TOTAL NUMBER OF ERRORS IN THE INTERVENTION GROUP WERE 86% LESS THAN IN THE CONTROL GROUP*

![Bar chart showing comparison between intervention and control groups.](chart.png)

*Baseline number of patients: Control group n=68, Intervention group n=78


**KEY CAPABILITIES**

**Data collection:** Data relating to patients’ home medication regimens and outpatient clinic plans were collected.

**Technical capacity:** Much of the intervention relied on changes to both the physician and pharmacist order entry systems. It took a working knowledge of the hospital computer systems, processes, and culture to identify the problem and to develop solutions. Regular review of systems is required based on HIV specialty evolvement, as this can quickly become outdated.

**Multiple stakeholder engagement:** Errors occurred at both the prescribing and dispensing stages, so interventions targeted both physician and pharmacist behaviour.

Sources: Daniels et al. 2012; Daniels 2012.
PREVENT MEDICATION ERRORS: CASE STUDY 12 – AUSTRALIA

Australia made efforts to reduce transcription errors through eTP (Electronic Transfer of Prescriptions)

BACKGROUND

Transcription errors between prescribers and pharmacies can be reduced through an electronic Prescription Exchange Service (PES). The Pharmacy Guild of Australia and Fred Health spearheaded the initiative from a commercial point of view, along with one other company (Medisecure) that also provided a PES. Funding was allocated through the Fifth Community Pharmacy Agreement between the Guild and the Australian Commonwealth Government.

INTERVENTIONS

The main impetus of the initiative was to utilise the latest computer and Internet technology to replace the traditional paper-based prescription forms with electronic transfer of prescriptions (eTP). This was done as an intermediate step towards a completely paperless prescription system, and to prepare for medication records to form a part of the national Patient Controlled Electronic Health Record, which is due to start on 1 July 2012. A national electronic prescribing platform was built over the course of one year.

Unique barcodes are printed onto participating doctors’ paper prescriptions using their existing software. The e-prescription is encrypted and sent securely to the PES using existing HeSA Public Key Infrastructure certificates held by all pharmacies and doctors. The patient takes the e-prescription to the pharmacy and the barcode is scanned by the pharmacist. The prescription details are downloaded to the dispensing software.

OUTCOMES

• It is cost neutral for pharmacies to use the service. The PES transaction fee is equal to the incentive payment that pharmacies receive under the Fifth Community Pharmacy Agreement Electronic Prescription Fee.

• There are no outcome/results data from post-intervention as this data was not collected. However, anecdotally there are reports that transcription accuracy has increased.

• Around 65% of pharmacies and 20% of prescribers are active users of eTP at this point. The fact that many prescribers have not registered or are not active users is currently a barrier to the full success of the system. Financial incentives are required for prescribers to ‘turn on’ electronic prescriptions in their prescribing software.
**KEY CAPABILITIES**

**Public-private partnerships:** Fred Health (IT producer) and Microsoft Australia partnered with public sector agencies to develop and produce the software.

**Involvement of multiple stakeholders:** Health IT specialists regularly consulted with pharmacists, GPs, and other medical practitioners during software development.

_Sources: Armstrong 2012; The Pharmacy Guild of Australia 2010._
**Sultan Qaboos University Hospital uses methods that are not resource intensive to reduce medication errors**

**BACKGROUND**

Look Alike, Sound Alike medications (LASA) are medications with names that look or sound alike, leading to avoidable mix-ups. These also include medications with similar packaging. Sultan Qaboos University Hospital (SQUH) is a 500-bed tertiary care hospital in Oman that saw increases in LASA-related errors, compromising patient care.

**INTERVENTIONS**

Pharmacists found 38 pairs of confusing names as well as 99 medications with similar packaging in the hospital formulary. A ‘Red Alert’ sticker was placed on LASA medications and shelves, similar medications were placed on different shelves, and suppliers with different packaging were used. Also, a ‘Tall man’ lettering system was introduced to differentiate medications so that the differentiating letters are all uppercase (e.g., PenecillAMINE vs. penicillIN). Educational posters were placed in the pharmacy and wards to remind pharmacists, clinicians, and nurses of the most commonly confused medications. Nurses were trained to be alert to LASA medications.

**OUTCOMES**

- QUH saw a shift in preventable medication errors; a large percentage of physicians, nurses, and pharmacists began double-checking medications. This was supported by the hospital’s ‘no blame’ culture of error reporting.
- SQUH is now engaged in an audit to examine the quantitative evidence regarding error reduction as a result of the Red Alert policy.
- Within a few days of introducing Tall man letters, there were 0% prescriptions with such errors.

The success of Sultan Qaboos University Hospital in reducing medication errors did not come without challenges. A high turnover of nurses meant that new staff frequently had to be trained on the program. The placement of the Red Alert label on prescription bottles had an initial alerting effect, which was reduced over time. Also, it was not possible for the hospital to print the Tall man lettering on the dispensed bottles. In spite of such challenges, medication errors were reduced; other hospitals can easily apply these small changes to achieve similar improvements.
**KEY CAPABILITIES**

**Multiple stakeholder buy-in:** Physicians, nurses, and pharmacists were all needed for successful intervention. Implementation was predicated upon erecting multiple checkpoints along the care pathway.

**Involved pharmacists:** Pharmacists led this intervention, and were responsible for reviewing the hospital’s formulary and double-checking all medications before dispensing.

*Sources: Al-Zadjali et al. 2011; Al-Zadjali 2012.*
Background analysis

**CONTEXT: DEFINING THE PROBLEM**

The main concern with medication errors are adverse drug events that cause negative patient health outcomes and induce resource utilisation costs (e.g., hospitalisations).

**Medication error:** Any error occurring in the medication-use process (Bates et al. 1995a). Examples include wrong dosage prescribed, wrong dosage administered for a prescribed medication, or failure to give (by the provider) or take (by the patient) a medication (Aspden et al. 2007).

**Adverse drug event (AE):** Any injury due to medication (Bates et al. 1995b). Examples include a wrong dosage leading to injury (e.g., rash, confusion, or loss of function) or an allergic reaction occurring in a patient not known to be allergic to a given medication (Aspden et al. 2007).

It is important to distinguish between preventable and nonpreventable AEs. Medication errors only refer to incidents where both harm was registered and an error was made (National Patient Safety Agency 2007). The Institute of Medicine contends that at least 25% of all medication errors are considered preventable (Aspden et al. 2007). Furthermore, a Dutch study contends that half of the medication related hospitalizations are preventable (Leendertse et al. 2008). The focus of this analysis is on these preventable adverse events (e.g., a patient given medication to which they have known allergies, given medication at 10x recommended dose, or given correct medication via wrong route of administration).

There are four processes that drive adverse events from medication errors: prescribing, preparation/dispensing, administration, and monitoring. Data from both country-level analyses and smaller scale hospital-level surveys show that errors are most likely to occur during administration, prescribing, and preparation/dispensing.

- Country-level data from the UK show that in 2007, 50% of medication errors occurred in the administration phase, 18% in preparing/dispensing, 16% in prescribing, 5% in monitoring and 12% in other across all care settings (National Patient Safety Agency 2007).

- A study of medication errors at The Johns Hopkins Medical Center found that of all errors reported, 41% were due to administration errors, 30% to prescribing errors, and 24% to preparation/dispensing errors (Miller et al. 2006).

- It should be noted, however, that because the data are skewed towards reporting in inpatient settings, it is likely that the overall percentages of prescribing errors (a primary source of errors in outpatient settings) are underrepresented in the data (Gandhi et al. 2005; Weingart et al. 2000).

Each process has a system in which many parameters are prone to error.

1. **Prescribing:** Involves clinical analysis; selection of a particular drug, dose, and regimen; documentation of the order; and transmission of the order to the dispensary/pharmacy. Examples of potential errors include:

   - Failure to notice a patient’s history of allergy to the prescribed drug class or missing critical information about a patient’s known drug allergies.
   - Use of the wrong drug name (e.g., sound-alike or look-alike names), wrong route of administration (e.g., intramuscular vs. intravenous injection), or wrong abbreviation (e.g., “qd” [every day] instead of “qid” [4 times per day]).
   - Incorrect dosage calculations, including wrongly placed decimal point and wrong rate, frequency, or unit of measure.

Causes of prescribing errors include:

- Incomplete or untimely access to the most recent and comprehensive drug information (Lesar et al. 1997).
- Incomplete medical history – the patient may fail to disclose all of his/her medications and provider may forget to ask about known drug allergies (Smith et al. 2005).
- Poorly handwritten prescription orders (O’Shea 1999).
Evidence from recent research in Malaysia by the Universiti Sains Malaysia demonstrates that 67% of medication errors by assistant medical officers were due to illegible handwriting, wrong use of abbreviations, and incomplete prescriptions rather than decision errors such as wrong indications, contraindications, drug-drug interactions, or other drug-related errors (Hassali et al. 2011).

2. Preparation and dispensing: The process by which a pharmacist prepares and dispenses medicines for consumption. Errors are most likely to occur when the wrong dose is dispensed to a patient. Example of a potential error: Patient dispensed morphine (Oramorph) 100mg/5ml UDVs instead of prescribed morphine (Oramorph) 10mg/5ml UDVs. The patient took two of these UDVs resulting in the patient’s death.

Causes of preparation and dispensing errors include:

- Failure by physicians and pharmacists to double-check orders, medication, and labels.
- High workload/low staffing (Roberts et al. 2002).
- Interruptions and distractions are both associated with significantly higher error rates in pharmaceutical care settings (Flynn et al. 1999).

3. Administration: Refers to the process of treating the patient with the dispensed pharmaceutical product. Examples of potential errors include:

- Administering the patient the incorrect dose of a particular drug.
- Administering the incorrect drug.
- Administering the drug via the incorrect route.

Causes of administration errors include:

- Miscommunication during the administration process as a result of errors in the transcribing of oral or written orders (e.g., intravenous medicines are often dosed and prepared on the floor, as opposed to oral medications, which are most often dispensed by dose through the pharmacy).
- Miscalculating medication dosages can result from the complexity of drug protocols, the need to confront emergent circumstances, and the increasing workload of hospital nurses (Fields and Peterman 2005; Jenkins and Elliott 2004).
- For example, evidence from a teaching hospital in Beijing, China, demonstrated the high probability of medication errors from intravenous medication administration. An analysis of medication administration records revealed a 13.39% medication error rate, primarily from the wrong dose, drug, and route of administration (Chu et al. 2011).

4. Monitoring: Refers to obtaining and evaluating clinical indicators and other relevant information to determine a drug’s effect in an individual patient (Knowlton and Penna 2003). Examples of errors associated with monitoring include wrong blood test results written in the physician’s notes, resulting in unintentional or inappropriate treatment such as prescribing of antibiotics due to the written error may cause patient severe harm such as renal failure.

IMPACT ASSESSMENT

Though estimates vary across study and country, medication errors are responsible for millions of adverse events worldwide. Among the sources investigated, the majority cite acute care as the source of most medicine-related incidents, followed by primary care. In the UK, the NHS reported a total of 72,482 medication errors in 2007 (National Patient Safety Agency 2007). In the US, the IOM estimates that medication errors harm at least 1.5 million people every year (United States Institute of Medicine 2007). While macro-level country data were not available, evidence from Japan (Morimoto et al. 2011), Australia (Runciman et al. 2003), and Spain (Carrasco-Garrido et al. 2010) were consistent with medication error rates (per hospital) in both the UK and the US.

These medication errors not only affect the lives of patients but also come at significant financial cost to healthcare systems. Medication errors often result in rehospitalisation or increased time spent in the hospital by those who experienced the AE while already hospitalised. Hospitals and healthcare systems then incur significant financial cost associated with additional treatments and rehospitalisations (Pinilla et al. 2006).
At the country level, these additional expenses total billions of dollars.

- In 2007, the UK NHS estimated the direct cost of medication errors at 2Bn GBP, or ~2% of overall healthcare expenditures.

- According to the US-based National Priorities Partnership, medication errors come at a direct cost of 21Bn USD to hospitals, outpatient providers, and payers (National Quality Forum 2008). This constitutes 0.84% of overall healthcare spending.

- Data from Spain suggests an average of 275Mn EUR (in 2006) in direct costs related to medication errors, or approximately 0.35% of overall healthcare expenditures (Carrasco-Garrido et al. 2010).

- At the hospital level, data from Spain suggests that the average tertiary care facility can expect to spend at least 76,000 EUR per year, or 4,128 EUR per medication error (Pinilla et al. 2006).

- In a recent Dutch study, the average costs for a preventable medication-related hospital admission were calculated by summing the direct medical costs and the production losses of all the preventable admissions. Combining the medical costs and the costs of production losses resulted in average costs of €6009 for one, potentially preventable, medication-related hospital admission for all ages. Studies suggest a range of figures for the total number of hospital admissions due to medication errors resulting in 114 to 649 million Euros or approximately 1% of overall health expenditure in the Netherlands (Leendertse et al. 2011; Leendertse et al. 2008; Gaal et al. 2011; The Health Foundation 2011; Zegers et al. 2009).

Medication errors are subject to chronic problems with under-reporting. Most systems rely on voluntary reporting, though a number of factors (e.g., time pressures, fear of liability, lack of perceived benefit) provide sufficient disincentive to report (Fontanarosa et al. 2004). Reports of medication errors have been steadily increasing over time, suggesting that the data do not yet reflect the true parameter. In the UK, for example, the number of AEs reported increased ~136% in just the two-year span between 2005 and 2007 (National Patient Safety Agency 2007).

The vast majority of medication errors are reported in inpatient settings where data collection systems are significantly more robust. Less data are available from outpatient settings, where a substantial proportion of errors are nonetheless likely to take place (Hughes and Ortiz 2005). In 2007, just 12% of all reported errors (8,603) came from prescriptions in the primary care sector. They also reflected an outpatient error rate of just .001%, far below the expected percentage given in smaller, micro-level studies.
References

Al-Zadjali, B.A. Personal communication with Badiya Al-Zadjali, Sultan Qaboos University Hospital, Oman. Apr., 2012


Armstrong, S. Personal communication with Stephen Armstrong, The Pharmacy Guild of Australia, Australia. Apr., 2012


Daniels, L.M. Personal communication with Lindsay Daniels, University of North Carolina Hospitals, US. Apr., 2012


References continued


Fields, M. and Peterman, J. 2005. Intravenous medication safety system averts high-risk medication errors and provides actionable data. *Nursing Administration Quarterly, 29*, (1) 78


Hughes, R.G. and Ortiz, E. 2005. Medication errors: why they happen, and how they can be prevented. *AJN: The American Journal of Nursing, 105*, (3) 14


References continued


IV. Medicine use revisited: Six primary levers of opportunity

5. RIGHT MEDICINE TO THE RIGHT PATIENT

Use low-cost generics where available

Suboptimal generic use contributes 6% of the world’s total avoidable cost due to suboptimal medicine use.
5. RIGHT MEDICINE TO THE RIGHT PATIENT: USE LOW-COST GENERICS WHERE AVAILABLE

Suboptimal generic use contributes 6% of the world’s total avoidable cost.

A total of 0.5% of global total health expenditure (THE), or 308bn USD worldwide, can be avoided from optimal generic use.

Generic use implies greater use of lower-cost generic medicines that drive cost savings in the health system without compromising quality of care and health outcomes.

The opportunity to gain additional savings from generics depends on affordability, medicine intensity, and infrastructure. This is why higher-income countries have less to gain than lower income countries. Competitive dynamics, demand, and generic awareness has made many of these countries ripe for a safe generic industry. In many other countries with less regulation and reduced medicine access, generics in general tend to be more expensive and brand loyalty prevents low-cost generic use.

Figure 18 below provides a snapshot summary of the relative avoidable costs out of THE. Data and respected ranges were estimated based on a combination of estimated and real values as well as data reliability. Global average values are weighted by country total health expenditure.

Ministerial relevance and recommendations

- Unbranded generic medicines are usually less costly than the original branded product or branded generics.
- Consequently, reassessing prescribing practices after patent expiry of the original product can drive savings in the health system.

FIGURE 18: AVOIDABLE COSTS (% OF THE) AT THE COUNTRY LEVEL

Source: IMS MIDAS, 2009 and 2011; World Bank 2009; WHO 2009; USD in 2011; Please see methodology section for details on global calculations which include 186 countries.
• Value can be added by a reassessment of the volume, prescribing practices, and to a limited degree price of medicines across unbranded generics, original-manufacturer branded generics, and branded generics.

• In this section, it is assumed health outcomes may improve if patients have access to quality medicines. Otherwise, outcomes are assumed to be as good as the intended quality of the medicines.

• Savings accrued through greater generic use are driven by margins within different parts of the supply chain (e.g., pharmacists, wholesalers, providers).

• Therefore, a comprehensive understanding of the economics across the supply chain is essential to determine a relevant policy strategy. Once this is done, Ministers can investigate greater uptake of unbranded generic medicines without undermining quality of care and/or can consider policies to drive price competition.

• Potential savings must also be seen in the context of how far countries have come in generic consumption over time, and how much further they can go given different policy priorities such as security of supply, quality, pricing, medicine access, proliferation of a domestic generics industry, and regulatory oversight.

Policymakers are also recommended to consider policy revisions in this area with sensitivity to medicine initiation vs. switching. Switching medicines based on savings from generic use may be risky for patient adherence, and consequently for efficacy. For example, the formulation or the delivery device (such as respiratory devices) can influence therapeutic efficacy in certain indications. For some patients, trusting the brand can be important with respect to effects.

HIGH-LEVEL RECOMMENDATIONS FOR THE MINISTERIAL AUDIENCE

Recommendations must be considered in light of each country’s current situation with respect to generic medicine use. Each country in the world differs on their starting point in this area, and consequently in the opportunity for cost savings on medicines after patent expiry. Most countries have made large strides over the last decade in revising generic policies. Compared with other levers, this area is vast, including nationally-driven policy options with demonstrated evidence across a wide range of countries. Therefore, countries are well positioned to learn from one another and leverage experiences to realise further savings.

In this section, a distinction is made between branded generics and unbranded generic medicines after patent expiry. For the purposes of this report, ‘branded generics’ refers to the combination of originator and branded medicines, while ‘unbranded generics’ refers to never-protected medicines after patent expiry. These medicines are referred to by their International Nonproprietary Name (INN) and are usually less expensive than branded medicines. The combination of branded and unbranded generics makes up the unprotected medicine market after patent expiry. It is worth noting that there is also a price and volume difference within the branded generic medicine group between originator medicines after expiry and new branded generic entrants. However, given the consistent price difference between branded and unbranded medicines, the focus is on these two groups only.

The reason this distinction is made is because price differentials among these medicines, as well as their volume penetration, drive the potential savings countries can expect to obtain. Generally, if price differentials are high, competition is limited and savings primarily can be derived from greater use of lower-cost unbranded generics. Supply-side incentives such as generic substitution can play a role in this scenario. Countries such as the US, Canada, Germany, Russia, and Brazil exemplify this situation, with over 70% of volume penetration in the unprotected market from unbranded generics, but relatively high price differentials. Such countries can also consider pricing policy changes to reduce the pricing differential.

If price differentials are low, supply-side incentives will drive whether or not volumes realize savings. Additionally, countries can consider promoting greater competition to reassess prices. Countries such as the UK and Australia have different policy
and incentive mechanisms in place to drive high volumes of safe, low-cost generic medicines, but both have attained over 70% of generic volume penetration from unbranded medicines post expiry and have incurred savings from generic substitution. Countries with low price differentials and low volumes such as Austria and France would also have a low opportunity for savings from substitution and can promote greater competition to reassess prices.

Figure 19 provides an overview of potential recommendations based on price differentials between branded and unbranded generics.

The following tables show the menu of options countries can consider depending on whether they would like to reassess pricing policies, volumes, or both.

**FIGURE 19: SUMMARISED COUNTRY RECOMMENDATIONS IN THE UNPROTECTED MARKET**

<table>
<thead>
<tr>
<th>Price differential between branded and unbranded generics</th>
<th>LOW</th>
<th>HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lows and highs for price differentials and volumes are relative to the EU5 average (.30 $USD per standard unit in 2011 and 68% volume share of unbranded medicines)</td>
<td>The opportunity for savings from substitution in this group is low. However, it implies that countries in this quadrant can promote greater competition to reassess prices. E.g., Austria, France</td>
<td>Countries already have policy regulation and/or competition to keep price differentials low. Countries also have usage-related incentives in place to use more unbranded medicines. The opportunity for savings from substitution in this group is low. While supply-side measures are in place to ensure high generic uptake, prices may be reassessed through greater competition. E.g., UK, Australia</td>
</tr>
<tr>
<td></td>
<td>Countries would need to introduce supply-side measures to increase the volumes of lower cost medicines. E.g., Japan, Ireland</td>
<td>Countries have policies in place to incentivise use of lower cost medicines. Countries may promote greater competition to reassess prices. E.g., Canada, Germany, Netherlands, US, Russia, Brazil</td>
</tr>
</tbody>
</table>

**Source:** IMS Institute for Healthcare Informatics, 2012.
# RECOMMENDATIONS DEPEND ON CURRENT COUNTRY CIRCUMSTANCES: PRICING POLICY OPTIONS

<table>
<thead>
<tr>
<th>POTENTIAL MOH INTERVENTIONS</th>
<th>REFERENCE POINT</th>
<th>SPEND</th>
<th>HEALTH OUTCOME</th>
<th>TIME SCALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess distribution chain: Manufacturer prices are low but not passed on to payers due to retail margins and mark-ups across pharmacists</td>
<td>UK (clawback mechanisms)</td>
<td>Low cost</td>
<td>Low</td>
<td>0-2 years</td>
</tr>
<tr>
<td>Revise competition policies: Local and/or regional payers can be empowered to negotiate for the insured or their population. (Caveat: policymakers should ensure that savings are incurred at the national level with regional payers/insurers managing negotiations with manufacturers)</td>
<td>Germany (sickness fund tenders), Netherlands, Denmark</td>
<td>Low cost</td>
<td>Low</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Revise regulation: Fixed rules such as direct price regulation or reference pricing for generics may keep prices high</td>
<td>Italy, France (as examples where price regulation exists)</td>
<td>Low cost</td>
<td>Medium</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Revise reimbursed prices for low-cost benchmark without undermining care quality and health outcomes</td>
<td>UK (frequent revisions on existing prices for pharmacists)</td>
<td>Low cost</td>
<td>Low</td>
<td>0-2 years</td>
</tr>
</tbody>
</table>
## POTENTIAL MOH INTERVENTIONS

<table>
<thead>
<tr>
<th>POTENTIAL MOH INTERVENTIONS</th>
<th>REFERENCE POINT</th>
<th>SPEND</th>
<th>HEALTH OUTCOME</th>
<th>TIME SCALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promote rapid market entry of generics</td>
<td>US</td>
<td>Low cost</td>
<td>Low</td>
<td>0-2 years</td>
</tr>
<tr>
<td>Promote prescription of generics through prescribing controls</td>
<td>UK, Brazil (hospitals only), Germany</td>
<td>Low cost</td>
<td>Low</td>
<td>0-2 years</td>
</tr>
<tr>
<td>Support INN prescribing as a common practice, though ensure pharmacist remuneration incentivises dispensing of low-cost generic medicines</td>
<td>Germany, Spain, Switzerland, UK</td>
<td>Low cost</td>
<td>Medium</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Implement financial incentives that support generic dispensing (e.g., align remuneration to pharmacists to encourage dispensing)</td>
<td>Canada, France, Spain, Switzerland, UK, Germany</td>
<td>High cost</td>
<td>Medium</td>
<td>0-2 years</td>
</tr>
<tr>
<td>Allow for generic substitution in pharmacies</td>
<td>Canada, France, Germany, Switzerland</td>
<td>Low cost</td>
<td>Medium</td>
<td>0-2 years</td>
</tr>
<tr>
<td>Campaign to ensure acceptability of generics among public</td>
<td>Australia, US</td>
<td>Moderate cost</td>
<td>Low</td>
<td>3-5 years</td>
</tr>
</tbody>
</table>
Basis for recommendations: Interventions and policy options

OPTIMAL GENERIC USE: IS IT ABOUT MEDICINE PRICES, VOLUMES, OR PRESCRIBING PRACTICES?

There are a number of policy tools that can drive generic promotion and higher use of lower-cost generic medicines. However, there is no set guidance on how to achieve optimal use of lower-cost generics through prices and volumes. To identify which tools are most appropriate, policymakers must consider trade-offs with respect to security of supply (e.g., ensuring shortages do not occur), quality, and price. These trade-offs are underpinned by larger, macroeconomic dynamics such as competition and interests of the domestic industry, affordability of medicines in the population, and regulatory mechanisms to ensure medicine registration, tracking of use, and quality oversight. Quality is a paramount consideration: it may be undermined without appropriate regulatory mechanisms. Figure 20 summarises these dynamics.

Interventions can target pricing policy to reduce prices and/or to increase volumes. One of the critical factors with respect to pricing policy is the degree to which pricing rules support competition. For example, Denmark, the UK, and the US encourage competition without price regulation. This fosters competition and drives down prices. Other countries such as Italy and France induce higher prices as they are generally determined through price regulation as a percentage below the price of a reference product. CNAMTS, the main health insurance fund in France, recently conducted an analysis that confirmed France’s generic medicine prices to be higher than those in Germany, Spain, the UK, and the Netherlands. In January 2012, France tried to introduce tenders (like those in Germany) or give pharmacists an opportunity to earn high margins on generics by negotiating lower purchase prices with manufacturers (similar to the UK and the Netherlands) but efforts have been stalled by the Parliament (IMS Health 2011).

FIGURE 20: MOST COUNTRIES CONFRONT TRADE-OFFS AMONG SEVERAL FACTORS TO MANAGE THE GENERIC INDUSTRY

- Most factors optimised: UK, Germany, Canada, US
- Supply high and pricing low but substandard quality: India, China, Egypt
- Supply and quality but suboptimal price: Ireland, France, Austria
- In economies with high out-of-pocket spending, affordability and access to medicines may or may not be a factor in generics policymaking
- Less government spending on medicines means greater branded generic promotion by manufacturers towards physicians and pharmacists, pushing higher prices to patients
- Preference for domestic industries and import restrictions drive up price and limit access to the population

Many governments use supply-side policies to influence different stakeholders, primarily pharmacists and prescribers in generic use. Figures 21 and 22 demonstrate the variety of policy interventions at the disposal of governments to incentivise generic use.

In Canada and Germany, mandatory generic substitution only exists in the public-funded sector. In France, GPs are encouraged to sign performance-related contracts with health insurers that include targets for generics prescribing. However, IMS Health research from 2011 found that there has been some resistance from pharmacists to substitute due to safety concerns as a result of a few warning notices from regulators. This analysis does not represent regional, in-country variation that may exist in multilingual countries such as Switzerland.

Prescribing by generic brand over the originator generic may not necessarily be favourable if branded generics have higher prices. While this is not a popular lever among high-income countries, most middle-income countries encourage it, as shown in Figure 22.
In general, these countries have many producers of branded generics (not originators) and strong brand loyalty among patients. While encouraging branded generic use may seem optimal, they may be more expensive than originator and/or nonbranded generics. There are a few reasons for this: with patients paying directly for medicines in most of these countries, companies spend more on promotion and marketing, which are required to establish and differentiate one branded generic from another.

The analysis in Figure 22 middle-income country analysis demonstrates other complexities. Saudi Arabia prioritises domestic industry and restricts imports. Doctors also receive financial incentives from local companies to prescribe specific brands. In Brazil, patient affordability is traded against the bargaining power of physicians and pharmacists with manufacturers. Although patients pay for the vast majority of medicines out-of-pocket, generic prescribing rates of unbranded generics remain low in the retail sector given the lack of prescribing control and physician incentives from manufacturers to provide higher-cost medicines. The latter trend is also
common in Egypt and China, where pharmacists and physicians primarily gain from financial incentives provided by local generics companies. These mechanisms set higher generic prices and counteract patients’ ability to afford medicines.

**Entry of never-protected generics** after patent expiry varies among countries, yet can induce savings, as reflected in the percentage of potential generic savings across countries. Governments can ensure that generics enter the market quickly after patent expiry through legislation similar to the Hatch-Waxman Act in the US or the Bolar provisions in the EU. These provide manufacturers with the ability to develop generics in advance of patent expiry. In the US, there are three main reasons for rapid generic entry: first, manufacturers can develop and manufacture generics before patient expiry. Second, generic manufacturers challenge companies with original products on their existing patents through litigation; the first manufacturer to win or receive a settlement (companies may work together or negotiate the expiry date) will receive 180 days of exclusivity after expiry. Finally, private insurance companies and pharmacy benefit managers (third party administrators of prescription drug programmes that process prescription claims for insurers) negotiate discounts and reduced prices with manufacturers. These dynamics incentivise aggressive generic company-led litigation and rapid market entry.

In the EU, the provisions exclude manufacturing, which means that companies are unable to physically produce medicines until approval is granted. Consequently, entry, registration, and reimbursement times still differ across countries. The bottom line is that different economies and price-setting mechanisms in countries will impact brand erosion after expiry. This depends on price differentials, the returns generic companies can expect, and market forces dictating speed to market.

**Patient education** can help alleviate some of the concerns with generic use between patients and prescribers. For patients, consumer education about the efficacy and value of generics has been proven to work. Educational campaigns targeting provider-led communication about generics and comfort with generic substitution has been proven to increase generic use in the US (Shrank et al. 2009). In 2008, Australia’s National Prescribing Service launched a national awareness campaign on generics that included educational pamphlets and TV commercials, targeting both patients and physicians. The campaign focused on people over age 50 and those with chronic conditions as well as their caregivers, and included three phases:

- Phase 1 – Rescreening of generic medicine TV advertisements from 2007.
- Phase 2 – Screening new TV advertisements supported by advertising, promotional, and public awareness activities.
- Phase 3 – A rollout of information and education for people from culturally and linguistically diverse backgrounds. The government spent ~$4.5 million USD on this campaign and consequently experienced a 29% increase in generic medicine awareness following Phase 1 advertisements, and a 5% increase (from an already high 72% baseline) in percentage of consumers who reported feeling confident about using generic medicines following Phase 2. The government considered this a success in increasing confidence among patients about the safety and benefits of generic use (Australia Government Department of Health Ageing, 2010).

Evidence from the US showed that patient education efforts reduce spending. For example, one generic education campaign employing targeted mailings increased generic conversion by 22%, at a savings of $88 USD per switch per year. Another extensive campaign that included mailings and advertisements dispelling myths about generics invested $1Mn USD in advertisements but saved an estimated $13Mn USD in reduced medicine cost (AARP Public Policy Institute 2008; Hoadley 2005; Stettin 2006).

Education efforts targeting physicians have also proven to increase generic use. For example, academic detailing (face-to-face interviews discussing individual GP prescribing) by the government on the benefits of generics have driven generic use in antipsychotic prescribing (AARP Public Policy Institute 2008; Benjamin et al. 2011). Physician training that includes generic use has also been proven to work, particularly in the UK where INN prescribing, while not mandatory, is extensively done due to the medical training curriculum and prescribing software.
While governments can take different steps to optimise generic use, consumer choice and preferences can overrule this due to brand loyalty either to branded generics or branded products in general. As mentioned above, manufacturer lobbying towards prescribers and pharmacists in countries where there is high out-of-pocket spending can inflate the burden on consumers. Therefore, government policies in some countries will always have their limits on how far generic optimisation can go and the impact it can realistically have.

Japan exemplifies a country with a deep history of strong brand culture, mitigating uptake of generics primarily related to physician discomfort in prescribing generics due to concerns about quality and efficacy. The government has implemented several initiatives to increase generic uptake from 20% share of market volume in 2009 to 23.5% in 2010. These include additional premiums hospitals can earn for using generic medicines and financial incentives for pharmacists to dispense generics (IMS PharmaQuery October 2011).

Country case studies: UK, Germany, Spain

Three country case studies demonstrate the evolution of policies and interventions that improved optimal generic use. Needless to say, each country has experienced challenges along the way. The UK and Germany have continuously been among the most mature generics markets in the world, suggesting there are lessons to be learned from their experiences. Brazil provides an example of a large, middle-income country. Finally, a commentary on Spain’s government royal decrees in September 2011 is provided. While they have a broader aim of reducing pharmaceutical expenditure at large, there is a generic focus as well.
USE LOW COST GENERICS WHERE AVAILABLE:
CASE STUDY 14 – UK

The UK has had a history of strong generic penetration with high volumes and low prices

BACKGROUND

In the 1970s, generics were only 10% to 20% cheaper than patented medicines. Since the 1980s, generic competition increased due to more players, driving down prices. The generics or ‘G’ computer button was also introduced in the 1980s to computerise INN prescribing. This transferred specific medicine choice to the pharmacist. The UK government actively pursues cost containment policies tied to performance where possible.

INTERVENTIONS

Pricing policies: The Department of Health reimburses pharmacies for medicines at the ‘Category M’ price (a weighted average manufacturer price after discounts). This applies to the majority of generics dispensed in primary care settings. Pricing trends are generally downwards given regular reimbursed price revisions and intense competition (10% to 50% of originator price).

Usage policies: It takes 10 to 14 months for registration and reimbursement. Providers have an 86% generic prescribing target, national prescribing guidelines, and formularies by Area Prescribing Committees that integrate across primary and secondary settings. Pharmacists retain profits from discounts on lower-priced generics at the ex-manufacturer level.

OUTCOMES

- Dynamic market competition.
- INN prescribing is common and most physicians do so even though it is not mandatory.
- Strong culture and acceptance of generic use, which takes a long time. Current results are from decades of interventions: 71% overall prescribing rate for generics.
- Generic volume penetration achieved is 14% above the EU5 average.

The UK system is not necessarily feasible throughout Europe. Prices are spiralling downwards yet profit margins still remain with pharmacists and are not fully delivered to the National Health Service (NHS). Since pharmacists have authority in medicine choice, the government has taken steps to take back some of the profit in the retail (or community) sector which is gained through discounts. These are known as ‘clawbacks,’ which recover monies from the supply chain. The payback rate is ~9%, though pharmacists still make a healthy profit after the clawbacks and Category M adjustments (~500Mn GBP per year). Additionally, the UK remunerates pharmacists for additional services and to compensate for losses from generic discounts.

As the role of community pharmacists expands into primary care provision through enhanced services (e.g., clinical medication review) to additional services (e.g., medicines management), pharmaceutical companies are increasingly developing a range of partnership programmes to support medicine compliance and chronic disease management. Efforts like these, and franchise systems whereby generic companies deal directly with pharmacies, have been forging stronger relationships between pharmacists and manufacturers (IMS Market Prognosis 2011).

Sources: IMS Health Market Prognosis, 2011.
Germany has introduced various generic entry policies in the last 10 years, becoming second to the UK among the EU5 in generic penetration

BACKGROUND

Germany started targeting generic use in 1989, with waves of interventions introduced to drive generic prescribing. Since 2003, health insurers (or sickness funds) have been free to negotiate volume and other rebates for generics and branded drugs directly with suppliers. Recent reforms in Germany (e.g., comprehensive reforms in 2007 and AMNOG reform in 2010) introduced cost containment mechanisms that have further affected generic penetration.

INTERVENTIONS

Pricing policies: Therapeutic reference pricing and tenders by sickness funds for discounted contracts have driven prices downwards.

Usage policies: It takes six to seven months for market access, including registration and reimbursement. Providers must follow national and regional prescribing guidelines that promote generic use. They are accountable to prescribing quotas (a certain percent of off-patent drugs should be prescribed) and preferences for products covered by discount contracts. This heightens emphasis on cost-effective prescribing. Payers have increased consolidation amongst each other, thereby increasing purchasing power to negotiate contracts with companies. Pharmacists have mandatory pharmacy substitution based on rebate agreements.

• Strong culture of generic use: 77% of products are now prescribed generically.
• 66% of generic market is rebate contracts.
• Penetration compared to EU5 is second to the UK (6% above EU average).
• Continued revision of prices by the government as comparison is made to the UK.

In the hospital sector, the Diagnostic Related Group (DRG) system incentivises hospitals to purchase medicines at the lowest price possible. The growing control of sickness funds over hospital costs will increase their influence on prescribing, especially where there is an overlap with the outpatient sector. However, significantly increased generic penetration in the hospital sector will be constrained by the originator brand offering favourable discounts to hospitals in order to drive usage.

Sources: IMS Market Prognosis Germany, 2011; Stolpe 2011.

OUTCOMES

In the retail sector, rebate contracts dominate what pharmacists can provide.

• Time 3 - 5 years
• Health outcome Low
• Spend level Moderate
Data collection and informatics that focus on monitoring and support of physician prescribing. Germany is implementing new software that uses a traffic light system to show how freely the product should be prescribed. This is tied to the prescribing quota, which refers to generics and products with discount contracts tied to volumes. The UK primary care prescribing system is informed by software that advises physicians on the cheapest alternative and substitutions. When GPs do not know the generic name, the computerised system automatically substitutes the generic.

Regulation and its enforcement in generic application review, guideline enforcement, and price control have been critical. For example, German sickness funds are obligated to negotiate rebates with manufacturers and maintain loyalty to selected manufacturers through a preference policy. Clawbacks in the UK prevent inflated pharmacist profits.

Training: In the UK, INN prescribing is encouraged during medical school education and has been consistently acknowledged for its impact on generic preferences among prescribers. In Germany, education exists at the national and state levels through web-based training. However, prescribing targets and financial penalties for excessive prescribing and/or financial targets not being met plays a greater role in Germany.
Impact of recent cost reduction reform with a focus on generics

BACKGROUND

In September 2011, Spain implemented a royal decree (RD 9/2011) as part of a series of cost containment efforts by the government since 2010. The decree includes a number of measures to control prescription volumes and price reductions (not surprising given that Spain is an OECD country with one of the highest number of prescriptions per capita, at 40% more than the average). INN prescribing as part of this decree is due to save Spain ~420 million EUR in the next year (~1% of total health expenditures based on 2010 numbers and 3% of total medicines budget) (OECD 2011).

INTERVENTIONS (sub-set of decree focusing only on generics).

INN prescribing is now mandatory and encompasses the following:

- The pharmacist will have to dispense only products at the lowest price (precios menores).
- Given an INN prescription, the pharmacist is allowed to dispense a generic or a brand provided that both are at the minimal price.

OUTCOMES

95% of the brands actually reduced their prices down to minimal price, which poses a challenge to generic companies. Therefore, INN prescribing may not necessarily push forth generics, as almost all off-patent brands are reducing their prices to be competitive. Early indications show a variable picture across the country as to the impact on generics vs. off-patent brands driven by regional implementation. Revisions in the reference pricing system also encourage this. All products representing the same compound must reduce prices as soon as the first generic is on the market, or lose reimbursement. Substantial variation exists on implementation among regions in their approach to INN prescribing. Andalucia has promoted INN since 2001 (with 80% of prescriptions by INN) while other regions have done so more recently with varying success and others do not actively advocate INN prescribing.

The increased role of the pharmacist as the decision maker may or may not drive generic uptake. Pharmacists will be looking at other service offerings to patients, perhaps in the realm of pharmaceutical care. They will focus more on margins, stock, and rotation of stock to maximise their revenues, and may be influenced by the efforts of off-patent brands to incentivise pharmacists to dispense the original brand.

Sources: IMS Institute for Healthcare Informatics, 2012; OECD 2011.

No health outcome, time or spend level is provided given the very recent implementation of this decree.
A FEW CAVEATS CONCERNING INCREASED USE OF LOWER-COST GENERICS

It is worth noting that where manufacturers negotiate prices with regional payers (e.g., sickness funds in Germany or the Netherlands), it is debatable whether central government realises those savings in the end. If margins are taken away from pharmacists, then whether or not they move to insurers instead remains a current point of contention among all stakeholders.

Finally, downward spiralling prices in the generic industry as has been witnessed in Europe may disincentivise generic production and competition. While industry considerations are out of scope for this report, governments trying to assess such policies could reasonably expect to be confronted with such challenges.

Background analysis

CONTEXT: DEFINING THE PROBLEM

Countries vary widely with respect to generic prices and volumes. Both need to be reassessed for optimal low-cost generic use that does not undermine quality of medicines and security of supply in the system. Price differentials between different generic medicines play a role. Where the prices of originator medicines and branded generic entrants are higher than unbranded generics, greater use of the latter can incur savings. For the purposes of this report, originator medicines and branded generic entrants are referred to as branded generics, while unprotected medicines are referred to as unbranded medicines. The weighted average of branded and originator generic medicine prices is usually higher than that of unbranded medicines.

In light of high (and in some cases, growing) health budgets, payers and policymakers can reassess policies influencing prescribing practices to drive cost savings without undermining health outcomes. In fact, by changing prescribing practices to increase spending on lower-cost medicines, payers may have more funding for higher priced medicines (e.g., newer targeted therapies such as biologic agents) and ensure their access to patients who may otherwise not obtain them. Such a consideration is only possible under two circumstances:

- If the unbranded generic costs less than the branded generic option (which is not always the case as it depends on which specific medicines are compared).
- If patients will accept and use generics. A change in prescribing practices is more likely to work at initiation rather than switching, since the latter risks nonadherence, and therefore worse outcomes.

Given this high variation, countries can assess prescribing practices to optimise for cost and quality in generics. Using low-cost generics where available is about using more unbranded generics in place of branded generics. The decision to substitute an unbranded generic for a branded generic may be by physicians or pharmacists, depending on the health system. Examples are common in NCD therapy areas. For lowering cholesterol, Zocor® can be substituted with generic simvastatin; for hypertension, Cozaar® can be substituted with generic losartan; and for depression, Cipralex® can be substituted with generic escitalopram. This approach can contain costs and increase the pool of funds available for innovative medicines in areas of unmet need that demand higher prices. This is only the case where alternatives are lower-cost and appropriate given patient health needs.

In France, volumes of unbranded medicines are relatively low compared to the EU5 average (69%) and so are price differentials.
Adjusting prices and volumes for generic use is not straightforward. Price, competition, medicine availability, and prescribing patterns all play a role in different ways. Pricing is particularly challenging because it is affected by a number of factors such as:

- The need for manufacturers to promote their product to physicians or pharmacists (e.g., particularly in countries with high out-of-pocket expenditure and brand loyalty).
- Health system support for competition to encourage price reduction (e.g., some countries have a preference for domestic industry that may drive up prices due to limited competition).
- Health system consideration for having a stable and secure medicine supply.

Additionally, realising the opportunity is a challenge with a breadth of complexities involving prescribers, pharmacists, and patients.

Prescribers may lack incentives to prescribe generics and/or are encouraged to use more expensive branded medicines. In markets where prescribers can choose the medicine (e.g., France, Brazil), they are often influenced by manufacturer detailing and brand loyalty from patients. In other countries, prescribers are not sufficiently informed about the value of generics and avoid generic prescribing as a result. For example, when the Abu Dhabi Health Authority introduced supply-side generic policies in March 2009 to incentivise physician prescribing, they faced resistance from prescribers because they had not bought into the value and were concerned about potential adverse effects or decreased effectiveness (Godman et al. 2011).

Prescriber resistance to generics is also evident in Malaysia. A recent study by Universiti Sains Malaysia revealed that only 4.6% of a prescriber sample in Penang correctly identified the Malaysian National Pharmaceutical Control Bureau’s bioequivalence standard for generic products. Prescribers showed misconceptions about the concepts of bioequivalence, efficacy, safety, and manufacturing standards of generic medicines (Hassali et al. 2011).

Pharmacists can also be economically disincentivised to dispense generics due to different remuneration policies. For example, in some countries such as Italy, pharmacists are financially penalised for dispensing cheaper, more cost-effective generic medicines (Bongers and Carradinha 2009; Dylst, Vulto, & Simoens 2012). Figure 23 provides an overview of pharmacist remuneration in a subset of European countries with regard to generic medicines.

Regressive margins and margin equalisation (guarantee of absolute margins) are commonly used, yet they are not effective if financial incentives for dispensing originator medicines are greater. Margin equalisation increases the price of generic medicines relative to originators so that price competitiveness is not achieved, and neither are savings to governments (Dylst et al. 2012).

In most countries (especially those in Europe), pharmaceutical companies compete by offering discounts to pharmacists, and potential savings from generic use are not captured. Discounts are confidential and related data are difficult to obtain. However, a study by the Norwegian Audit Office showed that prices and distribution margins of generic medicines are too high due to discounting practices (Norweigan National Audit Office 2009). The Netherlands and the UK have ‘clawbacks’ in place to recover some of these discounts but these interventions are limited: the size of actual discounts may be far greater than the clawback itself (Dylst et al. 2012). If discounts are outlawed, as has been
recently introduced in Poland, pharmacist remuneration must be reconsidered since they are historically an important source of income (Dylst et al. 2012).

Patients and consumers may prevent generic use if they lack confidence in the quality of generics. In some markets (e.g., China and India), patients have strong preferences for brands due to perceived better quality and fear of counterfeits. If adequate information is not provided on generic use and substitution, patients may not adhere to medication regimens due to concerns about bioequivalence and efficacy. This is exacerbated if a patient is on multiple medications. It is not uncommon for patients to stop taking their medicines if the medication color or size is changed (Kolata 2011).

Finally, the speed of entry is a barrier to greater generic use. In certain markets such as Portugal and some Central and Eastern European countries, generic medicine entry is often delayed, partly due to the need to gain pricing and reimbursement approval. An EU Pharmaceutical Sector Inquiry in 2008/09 by the European Commission found that the savings could be up to 20% higher for the 219 prescription medicines investigated if there were no delays in entry. There are differences between countries when it comes to generic capture after patent expiry. In the US, at 6 months generics capture over 80% of a brand’s volume vs. in Germany, where generics capture less than 50%. Percentages in Austria, Brazil, and South Africa are even lower. There are many reasons for delays, including litigations by originator companies and varied interpretations of regulations (e.g., patent linkage mechanism in Portugal whereby originators bring lawsuits before administrative courts in the name of process and product patent violations) (Sheppard 2011).

**IMPACT ASSESSMENT**

Many countries have increased the use of never-protected medicines by over 15%, with France in the lead in the following group of countries. Consequently, the potential for additional savings should be seen in light of recent achievements as shown in Figure 24.

However, countries can still take steps to increase use of lower-cost medicines through generic policies on volumes and prices without compromising health outcomes. In Japan, a 30% increase in generic substitution could result in ~2% of avoidable costs in total health expenditure. This amounts to ~88bn USD. In South Africa and Ireland, a similar analysis shows 0.6% and 0.5% respectively of avoidable costs from total health spending (IMS Health 2011 and 2012).

**FIGURE 24: MANY COUNTRIES HAVE COME FAR TO INCREASE USE OF LOWER-COST MEDICINES**

<table>
<thead>
<tr>
<th>Country</th>
<th>Absolute % change of unbranded generic penetration from 2006 to 2011</th>
<th>Relative standard unit* increase from 2006 to 2011, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRANCE</td>
<td>14.8</td>
<td>32%</td>
</tr>
<tr>
<td>US</td>
<td>14.2</td>
<td>19%</td>
</tr>
<tr>
<td>GERMANY</td>
<td>13.7</td>
<td>21%</td>
</tr>
<tr>
<td>CANADA</td>
<td>12.7</td>
<td>19%</td>
</tr>
<tr>
<td>AUSTRALIA</td>
<td>10.9</td>
<td>17%</td>
</tr>
<tr>
<td>NETHERLANDS</td>
<td>10.2</td>
<td>14%</td>
</tr>
<tr>
<td>JAPAN</td>
<td>9.0</td>
<td>24%</td>
</tr>
<tr>
<td>SWITZERLAND</td>
<td>7.2</td>
<td>14%</td>
</tr>
<tr>
<td>UK</td>
<td>5.9</td>
<td>9%</td>
</tr>
<tr>
<td>IRELAND</td>
<td>4.8</td>
<td>9%</td>
</tr>
<tr>
<td>SOUTH AFRICA</td>
<td>0.9</td>
<td>1%</td>
</tr>
<tr>
<td>BRAZIL</td>
<td>0.5</td>
<td>1%</td>
</tr>
<tr>
<td>RUSSIA</td>
<td>0.3</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

References


Australia Government: Department of Health Ageing. The Impact of PBS Reform: Report to Parliament on the National Health Amendment (Pharmaceutical Benefits Scheme)


Shrank, W.H., Cadarette, S.M., Cox, E., Fischer, M.A., Mehta, J., Brookhart, A.M., Avorn, J., and Choudhry, N.K. 2009. Is there a relationship between patient beliefs or communication about generic drugs and medication utilization? Medical Care, 47, (3) 319


IV. Medicine use revisited: Six primary levers of opportunity

6. RIGHT MEDICINE TO THE RIGHT PATIENT

Manage polypharmacy

Mismanaged polypharmacy contributes 4% of the world’s total avoidable cost due to suboptimal medicine use.
6. RIGHT MEDICINE TO THE RIGHT PATIENT: MANAGE POLYPHARMACY

Mismanaged polypharmacy contributes 4% of the world’s total avoidable spending due to suboptimal medicine use.

A total of 0.3% of global total health expenditure (THE), or 18Bn USD worldwide, can be avoided from managed polypharmacy.

Polypharmacy occurs when patients are taking two or more concurrent medicines. Taking multiple medicines may become problematic if there are more medicines prescribed than clinically necessary as there is a greater risk of adverse events, adverse effects from drug-drug interactions, and nonadherence due to a larger pill burden. This is more common among the elderly who often have multiple chronic conditions. In this chapter, the avoided costs from polypharmacy are considered in the context of patients with major polypharmacy who are taking at least five or more medicines concurrently. These patients risk severe adverse events with costly hospitalisations.

Figure 25 below provides a snapshot summary of the relative avoidable costs out of THE. Data and respected ranges were estimated based on a combination of estimated and real values as well as data reliability. Where there are only two points, the point estimate is the minimum. Global average values are weighted by country total health expenditure.

**FIGURE 25: AVOIDABLE COSTS (% OF THE) AT THE COUNTRY LEVEL**

Source: IMS MIDAS, 2009 and 2011; World Bank 2009; WHO 2009; USD in 2011; Please see methodology section for details on global calculations which include 186 countries
Ministerial relevance and recommendations

- Elderly people over age 65 and people with multiple illnesses are more likely to take more than two and often more than five concurrent medications, increasing the risk of avoidable adverse events that lead to downstream costs.

- Ministers of Health can support targeted interventions that strengthen the role of the pharmacist and physician to improve medicine management of such patients.

- Interventions are relatively straightforward to implement when the right patients are identified and the role of pharmacists is strengthened.

- Results and impact are quick: outcomes improve and downstream costs are avoided.

- There is spillover impact on other challenges in medicine use: nonadherence and medication errors are also indirectly addressed.

Basis for recommendations: Interventions and policy options

Policymakers have an indirect role to play in polypharmacy management through the support of stakeholders at the community level, primarily physicians and pharmacists. This is where actions can be taken to review and manage polypharmacy cases.

<table>
<thead>
<tr>
<th>POTENTIAL MOH INTERVENTIONS</th>
<th>REFERENCE POINT</th>
<th>SPEND</th>
<th>HEALTH OUTCOME</th>
<th>TIME SCALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invest in medical audits targeting elderly patients who are more likely to be taking multiple medicines</td>
<td>Netherlands, UK, Sweden, Germany</td>
<td>Moderate cost</td>
<td>High</td>
<td>0-2 years</td>
</tr>
<tr>
<td>Support greater role of pharmacists to own medicines management for patients and collaborate with physicians for revision</td>
<td>US (Health Alliance Plan), Australia (Home Medicines Review), Denmark (Pharmaceutical care for elderly)</td>
<td>Low cost</td>
<td>High</td>
<td>0-2 years</td>
</tr>
<tr>
<td>Encourage use of risk stratification process to identify patients and prepare targeted medicines management plan</td>
<td>US (Hyperpharmacotherapy assessment tool)</td>
<td>Low cost</td>
<td>High</td>
<td>0-2 years</td>
</tr>
</tbody>
</table>
Policymakers should invest in medical audits targeting elderly patients who are more likely to be taking multiple medicines. A robust medical audit system identifies gaps between clinical practice and guidelines and provides feedback for health professionals to prompt incremental performance improvement. The Cochrane Collaboration Group updates reviews on audit and feedback on healthcare practices (Jamtvedt 2007). The simulated patient visit technique has been used in several European countries (Germany, Netherlands, Belgium, and Sweden) for auditing purposes, where trained pharmacists simulate a patient and provide feedback to the colleague (Flottorp et al. 2010). Medical audits are widely used in the UK, where staff dedicated to medicines management use audits to improve medicine prescribing and consequently, manage polypharmacy (NHS 2008; UK Department of Health 2001).

**Physicians:**
- Ensure that a new medication is prescribed only when it is necessary or discontinue use of medicines that are potentially inappropriate.
- Review previous prescriptions through electronic medical record or interview with the patient before writing a new prescription (though assumption is that physicians and patients will understand one another).
- Manage care for individual patients and regularly review use of medications in community care sector.

Interventions targeting physicians need to consider the related challenge: Second guessing prescriptions of other doctors can be difficult unless prescribers have access to information systems that provide clear guidance on polypharmacy-related risks.

A hyperpharmacotherpay assessment tool was developed by Bushardt et al. to support clinicians in evaluating medicine therapies in a concise yet comprehensive way. The tool builds on Bergman-Evans’ Medication Management Outcome Monitor which is an evidence-based guideline specifically developed for older adults taking multiple medications (Bushardt et al. 2008). The same authors previously developed a check-list known as ‘Nine key questions to address polypharmacy’ to help clinicians manage medicines (Bushardt et al 2005). While additional research is needed to develop quantitative evidence, such a tool and similar checklist-like approaches have the potential to drive efficiencies in medicines management as they have in the past in other industries such as aviation (Gawande 2009).

**Pharmacists** in the primary and/or outpatient setting:
- Work in collaboration with physicians to optimise regimen (See Health Alliance Plan case study): Implementation of pharmacist interventions saved 4.16 USD per patient per month (Galt 1998). In another US-based study, the inclusion of pharmacists in the intensive care unit prevent 66% of AEs, which was estimated to save the hospital in the study approximately 270,000 USD per year (Leape et al. 1999).
- Conduct medical utilisation reviews (MUR): Pharmacists can play an active role in helping patients make comprehensive lists of prescription and over-the-counter medications; this can include dosage, frequency, strength, and duration of therapy. Pharmacists can actively help patients simplify drug administration, such as using single daily dosage regimens when possible and using combination drugs available in one pill when available (e.g., hypertension and angina). Pharmacists provide advice to improve clinical effectiveness of medication through better use. Supporting evidence exists from MUR (PSNC in the UK) and Home Medicines Reviews (HMR) in Australia.
- For pharmacists, second-guessing prescriptions can be difficult and time consuming. Knowledge, training, and access to information systems are crucial for pharmacists to help manage polypharmacy. From a patient perspective, dealing with multiple parties to understand how to appropriately take a complex medication regimen is challenging. A designated healthcare professional as one point person with the responsibility for the patient’s medication can make a difference. The patient is more likely to use medications appropriately if one healthcare provider monitors their use and outcomes, and oversees interactions with different providers.

**Country case studies: US, Denmark**

Two case studies are provided from the US and Denmark to demonstrate polypharmacy control through medicines therapy management (MTM).
Health Alliance Plan: Medication Therapy Management Programme helps improve quality of care while assuring cost-effectiveness of therapy options

BACKGROUND

The Medicare Modernization Act of 2003 included a requirement beginning in 2006 that Medicare Part D insurers provide MTM as part of their Medicare drug benefit programme to patients with multiple chronic diseases who are taking multiple medicines. This grew out of US evidence on the correlation between medication numbers and AEs (seven or more carries an 82% risk). From 20% to 30% of hospitalisations are due to AEs among the elderly over age 65. The Health Alliance Plan (HAP) is an insurer in Detroit, Michigan, with staff physician groups (35%) and community physicians (65%) who contract with them.

INTERVENTIONS

Interventions stemmed from a realisation that the overall healthcare approach had moved to a patient-centric approach and the medication therapy management programme (MTMP) should evolve from drug-centric to patient-centric. HAP developed its own methodology for MTMP data collection, data tracking, and outcome monitoring in 2006, and refined it each year. From 2006 to 2009, HAP enrolled ~1625 patients per year. On average, 20% were taking 20 unique medicines and the rest were taking between eight and 19 medicines. These included Medicare and retiree populations with similar risk factors. An ambulatory clinical pharmacist-led, patient-centric approach was applied: pharmacists led medication management and integrated with patients individually. Pharmacists listened to patients and integrated patients’ personal health goals with evidence-based medicines.
Outcomes improved in 5 main areas from 2006 to 2011

1 Pharmacist efficiency: By 2009, 90% of pharmacists spent 15 to 30 minutes with physicians, a 34% increase since 2006.

2 Medication interventions:
- 55% included changing drug therapy to improve efficacy.
- 45% included changing drug therapy to improve safety.

Polypharmacy-related interventions:
- 23% of the interventions involved changing drug dose/schedule.
- 15% of the interventions removed medicines prescribed but not needed or duplicate therapies.

3 Health outcomes: The ‘accepted’ MTMP enrollees with arthritis had a statistically significant reduction in gastrointestinal bleed rate compared to the ‘declined’ MTMP group. Within accepted MTMP enrollees with arthritis, significant reduction also was seen pre- to post-MTMP enrolment.
For three out of the six outcome measures analysed, patients enrolled into MTMP did better than those who had declined enrolment.

4 Patient satisfaction: A survey showed that 97% of enrollees who replied felt the pharmacist MTMP was helpful.

5 Cost avoidance: Cost savings over 2006 to 2009 was about 4.4Mn USD, a combination of 2.4Mn USD from prescription cost savings (16% reduction) and 2Mn USD from medical cost avoidance (21% reduction).

OVER FOUR YEARS OF IMPLEMENTATION, PHYSICIANS’ TIME HAS BEEN SIGNIFICANTLY SAVED DUE TO PHARMACIST INTERVENTION

Additionally, on average, pharmacists have reduced the amount of time spent per patient per year by 45 minutes.

Pharmacists now spend ~2 hours per patient per year (this may be slightly less than for patients on 20 or more unique medicines):
- ~30 minutes for medication concern investigation
- 1.5 hours per MTM case

MTMP IS AN EFFECTIVE METHOD TO IMPROVE POLYPHARMACY MANAGEMENT FROM AN EFFICACY AND SAFETY PERSPECTIVE

In a 2010 analysis of interventions, over 80% of recommended interventions have been implemented (e.g., physicians changed prescription drug regimen per pharmacist’s recommendations and/or patient changed nonprescription drug regimen per pharmacist’s recommendations).

Additionally, while the program works well in the HAP and Henry Ford Medical System, HAP clinical pharmacists also engage with physicians outside of the system regularly and have experienced similar uptake rates of interventions (~65% uptake of interventions). As the medical record system does not cover physicians outside the group, HAP cannot track outcomes in a similar way. Nevertheless, HAP pharmacists review medicine intake with complex patients regularly to monitor use.

A manual claims/chart review was conducted for the 2006 MTMP eligible population (enrollees vs. those who declined enrolment) to determine the program’s success in outcomes. For three of the six outcome measures analysed, patients enrolled in the HAP MTMP did better than those who had declined enrolment. For two of the six outcome measures analysed, patients enrolled in the HAP MTMP had similar outcomes compared with those who had declined enrolment. However, the trend is in the programme’s favour.

HAP has been building on this program through application of MTMP to the Patient Centred Medical Home (PCMH) with an ambulatory clinical pharmacist. Results of a 2010 study of complex cases (seven comorbidities per patient) with high risk of medication errors demonstrated better medicine use and cost avoidance due to reduced hospitalisations (new and readmissions), ED visits, and physician office visits.

**Adherence and medicine use improved...**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>On MTMP vs. Patients who declined (2006), % change before and after intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF-ACE/ARB</td>
<td>-3</td>
</tr>
<tr>
<td>CHF-B-blocker</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes insulin use</td>
<td>3  2</td>
</tr>
</tbody>
</table>

**...and so did health goals**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>On MTMP vs. Patients who declined (2006), % change before and after intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes-HbA1c&lt;7</td>
<td>-60</td>
</tr>
<tr>
<td>Arthritis-GI Bleed</td>
<td>0</td>
</tr>
<tr>
<td>CAD (Coronary artery disease) -LDL&lt;100</td>
<td>-6  6</td>
</tr>
</tbody>
</table>

**Data collection:** Pharmacy claims data by pharmacy benefit manager to monitor medicine use during intake and prepare to intervene accordingly depending on patient needs and outcomes.

**Multistakeholder engagement, particularly physician buy-in:** Collaboration of pharmacists, physicians and patients. Physicians welcomed having pharmacists either be based at their office or assist with medicine management offsite by phone due to the complexity of some patient cases. Pharmacists provide three key benefits for physicians: continuous medical education (regular updated information on medicine management and therapies); free time to ensure physicians handle less complex cases from a medicines management perspective; better equipped to handle medicine complexity of patient cases.

**Extensive use of telephones to substitute for face-to-face visits:** With patients and physicians, pharmacists primarily use the phone to communicate and discuss medication regimen changes. HAP discovered that: telephone use significantly saved travel and transaction time for pharmacists; patients are comfortable using the phone for follow-up; pharmacist productivity improved in terms of patient management (more patients can be followed in the same amount of time); and many of the senior population preferred the telephone service, which allowed for in-depth discussion on their medications without worrying about rides to and from home and the clinic.

**There are a few key challenges with implementation of such a program:**

**Continued support without demonstrating direct cost savings.** Cost savings and return on investment analyses from such programs may not be realised for years. Better medicine management prevents long-term hospitalisations which are difficult to measure and attribute to a program that took place years before.

**Limited best practice sharing between MTMPs in the US:** Given that these programs are implemented in different states, greater communication would be expected about outcome measures and best practices in implementation. Since PCPCC and other national pharmacy groups have started to communicate on this over the last few years, there has been more consistent outcomes across states.

*Sources: Zarowitz et al 2005; Pindolia 2009; Pindolia 2012.*
MANAGE POLYPHARMACY: CASE STUDY 18 – DENMARK

Denmark decreased hospitalisations and improved medicine intake through pharmacist-led, targeted services

BACKGROUND

Elderly people are more prone to health problems. They are prescribed more medicines and thus have an increased potential for drug-related problems. A baseline survey of elderly people in Denmark showed participants used an average of 6.8 prescription drugs, and one-third reported adverse effects from the drugs. The majority of medicine-related hospital admissions for this group are due to therapeutic failures. One-third of patients had challenges opening medicine packaging.

INTERVENTIONS

The Danish Pharmacy Assistants Association and the Association of Danish Pharmacists Development Fund initiated a pharmaceutical care programme based on actively identifying, solving, and preventing drug-related problems for selected customer groups. They started with a pilot known as Improving the Well-being of Elderly Patients via Community Pharmacy-based Provision of Pharmaceutical Care (1996-1999). This was part of PCNE (Pharmaceutical Care Network Europe), a collaborative project among seven countries supported by an EU grant. The project was carried out in 28 pharmacies in Denmark between 1996 and 1999 with the participation of 523 elderly medicine users age 65 years or older. It continues to exist today.

The programme focuses on patients over age 65 who take five or more prescriptions. When visiting pharmacies, they are offered a programme of structured counselling and quality assurance containing the following elements:

1. Technical medication check-up. All of the patients’ medicines are checked to identify and discard outdated and useless medicines. Patients are instructed in the practical use and handling of medicines;
2. A medicine regimen assessment and identification of medicine-related problems;
3. Patients are provided with a diary for self-monitoring at home;
4. A medication overview is provided regularly to patients that includes all their medicines. The overview is helpful to the patients and is a means of communication between pharmacists and other health professionals;
5. Patients receive individual counselling on problems associated with their medicine use. Following the first consultation, a personalised intervention and monitoring plan is formulated based on the patient’s individual needs. As a minimum, this would be followed up by an encounter every three months.

<table>
<thead>
<tr>
<th>Time</th>
<th>0 - 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health outcome</td>
<td>High</td>
</tr>
<tr>
<td>Spend level</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Over a period of 18 months, patients’ problems of swallowing medicines declined from 11% to 6%.

Patients’ confusion about when to take their medication fell from 4% to 2.5%.

Over 18 months, the programme saved an estimated 328Mn DKK (43.7Mn EUR).

Most importantly, the programme has been rolled out nationwide as part of the Danish Pharmacy Standard. In Denmark, 90% of pharmacies are now accredited to provide this service and are financially supported to do so by the national government. Some medication review services are paid for directly by patients or in contracts with municipal health administrations.

**KEY CAPABILITIES**

**Data collection:** Patient recruitment is conducted in pharmacies; clinical outcome data is collected in pharmacies; health insurance funds provide claims data.

**Multistakeholder engagement:** Collaboration is encouraged and supported between pharmacists and physicians. Physicians welcome pharmacists’ participation in medication management.

**Pharmacist education:** A manual of community pharmacy-based interventions was developed to help standardise activities carried out in different pharmacies. Pharmacists receive medicines management training based on the manual and are also trained in consultation and communication skills.


### OUTCOMES

<table>
<thead>
<tr>
<th>% hospitalization frequency</th>
<th>% of hospitalisation baseline vs. 18 months later</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group</td>
</tr>
<tr>
<td>% of hospitalisation baseline</td>
<td>40</td>
</tr>
<tr>
<td>% of hospitalisation 18 months later</td>
<td>36</td>
</tr>
</tbody>
</table>

HOSPITALISATION FREQUENCY FOR THE INTERVENTION GROUP DECREASED BY 9%, WHILE FREQUENCY FOR THE CONTROL GROUP INCREASED BY 6%.

Background analysis

CONTEXT: DEFINING THE PROBLEM

There is no consensus on how polypharmacy is defined. In the outpatient setting, polypharmacy is usually five or more medications, while in the inpatient setting polypharmacy can be as high as 10 medications (Junius-Walker et al. 2006; Viktil et al. 2007; Hilmer 2008). Community studies (Nottingham UK, Finland, the Netherlands, US, and Sweden) have documented the increase in the number of medicines per patient taken in primary care and prescribed during inpatient care over time (Gorard 2009; Rumble and Morgan 1994; Linjakumpu et al. 2002; Jylhä 1994; Stewart et al. 1991; Veehof et al. 2000; Silver and Lundborg 2005; Lernfelt et al. 2003; Blix et al. 2004). Polypharmacy has been increasing among patients in both community and hospital prescribing. Figure 26 demonstrates how patients over 60 years old are predominantly affected across different countries.

Polypharmacy is driven by several factors: new drug treatments, new indications for older drug treatments, and lower thresholds for diagnosing (e.g. diabetes, hypertension blood pressure). It is also driven by adverse effects from other treatments and a minimal focus in most health systems to reassess treatment needs over time. However, the greatest driver of polypharmacy management challenges is predominantly from people over age 60 with multiple conditions and prescriptions from different physicians.

Older people contribute disproportionately to medicine consumption. Based on recent statistics by the Kaiser Health Foundation, the average American adult aged 65 and over now takes 28 retail prescription medicines per year vs. 11.9 for those aged 19 to 64 (Kaiser Family Foundation 2012). In Canada, data from 2009 demonstrates that 63% of seniors had claims for more than five drug classes and 30% of those over 85 years old had claims for more than 10 (Canadian Institute for Health Information 2011). Elderly people take many of these medications for multiple chronic diseases such as hypertension, diabetes, Alzheimer’s disease, or cancer.

- According to recent data from Australia, 66% of participants in a nation-wide study aged 75 and older were taking five or more medicines. Most medicine intake was for long-term conditions such as hypertension and cardiovascular disease (Morgan et al. 2012).
- In the next 20 years, about 70% of all cancers diagnosed in the US will be in older adults (Barclay 2011).

FIGURE 26: PATIENTS >60 YEARS OLD ARE AT HIGH RISK OF MAJOR POLYPHARMACY*

<table>
<thead>
<tr>
<th>Country</th>
<th>&gt;60</th>
<th>40-59</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td></td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Netherlands</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
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<tr>
<td>Egypt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indonesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colombia</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Of patients >60 years old with two diseases, hypertension and diabetes are the most prevalent comorbidities regardless of country type (income levels)

They are also most prevalent in patients with three and four diseases

*Based on prescription data for seven countries. 
In a recent Canadian study among cancer patients, 92% of patients age 65 or older were taking a median of five prescribed medications before starting cancer treatment (Lees and Chan 2011); similar observations were made in US hospitals.

As the aging population increases disproportionately to other populations, it is expected that polypharmacy practice will also rise: there will be continued demand for different medications used to treat or delay chronic conditions and improve quality of life (World Health Professions Alliance 2002).

Mismanaged polypharmacy in the elderly is complicated by body composition changes that occur with advancing age. With aging, the percentage of muscle mass and body water decline as body lipids increase. The change in absorption mechanisms may cause reactions when different medicines have a compounding effect (Ginsberg et al. 2005). Certain medicines react differently due to metabolic changes in the elderly and increase the likelihood of adverse events if not carefully tracked and managed. The most common classes of medicine in which this is likely to occur are cardiovascular medicines, diuretics, nonopioid analgesics, antidiabetic agents, and anticoagulants (Zarowitz et al. 2005).

Mismanaged polypharmacy is particularly dangerous among patients with certain diseases such as cancer. Cancer therapy is often pre-empted by a previous medical history that requires a number of different medications, and by over-the-counter (OTC) and complementary and alternative medications (CAM). These medications have been found to trigger adverse events when combined with chemotherapy agents. Anticoagulants such as warfarin have been found to cause adverse drug reactions among cancer patients (Lees and Chan 2011).

**IMPACT ASSESSMENT**

When the complexity of medication regimens in polypharmacy is not managed well, AEs and additional spending are substantial risks. Multidrug regimens can cause confusion among dispensers due to similar names or labelling. Additionally, therapeutic duplication among different prescribers leads to inappropriate medication administration, often contributing to nonadherence. Complex regimens increase the risk of drug interactions (e.g., concurrent use of blood thinners and aspirin-like medicines, combined use of beta agonists for lungs and beta blockers for heart which cancel each other out) and cause adverse reactions. For example, AE frequency is 6% when taking two medicines, but 50% when taking more than five medicines and almost 100% when taking more than eight medicines (Bieszk et al. 2002).

Polypharmacy also causes avoidable spending, including the medication costs, hospitalisation costs due to AEs, and the cost of additional medication needed to treat AEs. Hospitalisation from AEs due to cardiac causes among the elderly are very common; in a number of these situations, the elderly are taking multiple medications which have not been assessed for appropriate use.

In one study from six EU countries, 15% of elderly taking on average seven medicines had one or more drug-disease interactions (common are aspirin and peptic ulcer, and calcium channel blocker and coronary heart disease) (Thomson 2008). Other interactions can be from drug-drug and drug-food interactions.

The economic impact of mismanaged polypharmacy is not negligible and is similar in the US and the UK. For example, in the US, costs due to hospitalisation, additional medication, and resource use can account for up to 8.7Bn USD (~0.3% of total health expenditures in 2010). In the UK, of the 4.8 million people over age 75, polypharmacy is prevalent in ~40% of patients. The total cost to the system can be as high as 727Mn USD (or ~0.3% of total health expenditures in 2010) (Thomson 2008; US Census Bureau 2010; IMS Institute for Healthcare Informatics 2012).

IMS Institute analysis suggests that in Singapore, mismanaged polypharmacy can incur costs as high as 105Mn USD (or ~2% of total health expenditures in 2010). Commonly prescribed medications include cardiovascular medications (19.6%), psychoactive medications (13.9%), gastrointestinal medications (14.2%), vitamins or nutritional supplements (15.9%), analgesics (6.4%), and sedating antihistamines (4.7%) (Mamun et al. 2004).
References


Gorard, D.A. 2006. Escalating polypharmacy. QJM: An International Journal of Medicine, 99, (11) 797-800


Herborg, H. Personal communication with Hanne Herborg, Pharmakon Denmark, Denmark. Apr., 2012.


Galt KA. 1998. Cost avoidance, acceptance, and outcomes associated with a pharmacotherapy consult clinic in a Veterans Affairs Medical Center. Pharmacotherapy, 18, (5) 1103-11


Linjakumpu, T., Hartikainen, S., Klaukka, T., Veijola, J., Kivela, S.L., and Isoaho, R. 2002. Use of medications and polypharmacy are increasing among the elderly. Journal of Clinical Epidemiology, 55, (8) 809-817


Pindolia, V.K. Personal communication with Vanita Pindolia, Health Alliance Plan, US. Apr., 2012


V. Medicine use revisited: Three secondary levers

1. RIGHT MEDICINE TO THE RIGHT PATIENT
Use expensive therapies selectively through predictive diagnostics

Personalised medicine and the related field of predictive diagnostics hold great promise for offering new approaches to the cost-effective delivery of care and improved health outcomes.
1. RIGHT MEDICINE TO THE RIGHT PATIENT: USE EXPENSIVE THERAPIES SELECTIVELY THROUGH PREDICTIVE DIAGNOSTICS

Ministerial relevance and recommendations

- This section provides Ministers of Health with a preliminary understanding of the personalised medicine space with respect to medicine use, particularly in specialised and high-cost areas such as oncology.

- Although investing in personalised medicines may not result in overall net cost savings, there are positive gains to be realised in terms of minimising suboptimal medicine use by targeting treatments to patients who will respond and improving health outcomes that can increase quality of life and result in productivity gains.

Personalised medicine and the related field of predictive diagnostics holds great promise for offering new approaches to the cost-effective delivery of care and improved health outcomes. However, because of the relative newness of this field and the absence of sufficient supporting data, it is difficult to provide the same kind of recommendations included in other portions of this report.

Basis for recommendations: Interventions and policy options

1. Fostering research and development through multistakeholder collaboration, transparency, and industry financial incentives.

The use of biomarkers enable budget impact to be mitigated and potential return to the health system to be improved. Countries are now (and will continue to be) in an improved position for industry collaboration in this area to identify how to incorporate these diagnostic modalities into existing paradigms and track use in patients. IMS Institute research shows that collaboration is needed across stakeholders (governments, providers, pharmaceutical companies, diagnostic organisations) in order to align incentives and address the challenges of developing new predictive diagnostics, bringing them to market and showing their clinical effectiveness (Davis et al. 2009; PricewaterhouseCoopers 2009).

For example, in the US, Medco Health Solutions, one of the country’s largest pharmacy benefits managers, announced a two-year research partnership with the US Food and Drug Administration (USFDA) to explore the link between genetics and the efficacy of prescription drugs (PricewaterhouseCoopers 2009). Furthermore, again in the US, C-Path is forging collaborations among the USFDA, academia, and industry to shorten the path for bringing new drugs, diagnostics, and medical devices to market (PricewaterhouseCoopers 2009). C-Path also collaborates with the USFDA, the European Medicines Agency (EMA), and multiple pharmaceutical companies to jointly address translational challenges.

2. Evaluating appropriate pricing and reimbursement schemes

Pricing and reimbursement schemes for predictive tests can influence treatment options. Currently, most pricing and reimbursement institutions’ processes differ between diagnostics and medicines. Going forward, greater communication among stakeholders (including policymakers, payers, and providers) can adequately assess the value of new predictive diagnostics given current and upcoming treatments.

Risk-sharing options can be considered from a reimbursement perspective. For example, when Oncotype DX®, a predictive diagnostic for breast cancer therapy was initially on the market, consumers had to pay out-of-pocket for the test. Only when sufficient clinical data was gathered to quantify potential cost savings did payers begin to reimburse for the test (PricewaterhouseCoopers 2009). While risk sharing may alleviate the budget impact, it requires monitoring and tracking of information, which is burdensome for physicians and payers alike. Administration-related costs would need to be considered.
3. Real-world evidence

There is a need to solidify and strengthen understanding of long-term impact and societal gains from real-world evidence. Currently, most observational studies are for safety and surveillance, not outcome tracking. However, outcome tracking can be vital: registries can be set up as observational studies with some statistical rigour to track outcomes. This has been done for Avastin® (bevacizumab) in the US, where registries that assess patient outcomes after more than a year demonstrated patient improvements in terms of quality of life and productivity over the long term. In the US, the patient registry by the Cystic Fibrosis Foundation has existed for more than 40 years, tracking patient characteristics and outcomes to inform policy (Cystic Fibrosis Foundation 2012).

Basis for recommendations: Interventions and policy options – Challenges

Although personalised medicines and predictive diagnostics are an emerging area with promising impacts on quality and costs, there are still barriers to overcome before widespread use, including understanding the budget impact of testing, addressing the lack of infrastructure to support testing, and overcoming clinical barriers. Other challenges are a lack of rigorous clinical evidence in terms of outcomes to support their use, and limited available data as they apply to very niche markets. This analysis draws on some of the latest critical thinking from IMS Health and IMS Consulting Group experience on predictive diagnostics and provides some insights into potential interventions that address these issues.

Challenge 1: Budget impact of testing patient populations

The question of who funds and covers the costs of testing is a key challenge. Uncertainty in funding and coverage, as well as the overwhelming cost of testing, are key issues for payers in the personalised medicine space. For example in the US, a coverage gap exists for genetic testing in some plans; in the EU, manufacturers often pay for testing initially and withdraw funding once the drug and diagnostics are well accepted, leaving the financial burden to the hospital or regional payer (e.g., Italy, Spain, UK).

New tests will be developed as targeted treatments become available for specific subsets of patients. The cumulative costs of such tests will increasingly become more of a challenge to payers. Furthermore, the costs of training providers on new diagnostics will be an additional expense.

Figure 27 exemplifies the increasing number of agents targeting different subpopulations in non-small-cell lung cancer (NSCLC).

An additional challenge in the context of low- and middle-income countries is utilisation of personalised medicines due to the overwhelming costs. This in turn may lead to compulsory licenses being issued for a cancer drug, as was the case in India (Sharma 2012). In China and other middle-income countries, affordability is likely to be a challenge. While a Her2 test for breast cancer costs between 12 and 15 USD, one Herceptin® cycle is 3,500 USD, a prohibitively high out-of-pocket cost for many patients (Gochenauer 2011).

Challenge 2: Lack of infrastructure to support predictive testing

As new tests enter the market, they often enter a technically undefined territory in terms of reimbursement systems (e.g., codes, DRGs, etc.). Office-based oncology specialists (e.g., in Germany) who are the primary contact for these patients find...
reimbursement tracking for such new tests administratively burdensome. Furthermore, laboratories have not seen increases in budget, which prohibits their ability to conduct these new tests.

Other logistical burdens, particularly for office-based specialists include requirements for patient transportation between office and lab site; the lack of protocols; and information challenges accessing, transferring and interpreting results of predictive diagnostic tests.

Challenge 3: Clinical barriers and outcome ambiguity

While clinicians generally welcome the use targeted therapies based on the likelihood of patient response, there are several clinical concerns surrounding tissue acquisition, such as what type of tissue sample is tested, whether blood or biopsy; how the tissue is obtained, as an invasive procedure carries additional risks for the patient; how much tissue is required for testing; and what special conditions may be required for transporting the tissue to the testing site.

Outcome ambiguity is also a challenge. For example, the probability of suboptimal treatment may increase depending on the pricing and reimbursement schemes for tests. For instance, if a new treatment is available on the market with potentially lower adverse events but requires testing for which there is no budget, physicians may prescribe older, suboptimal treatments. This was the case with Tarceva® (erlotinib), a treatment for NSCLC that initially had a predictive diagnostic but was removed from the market in Europe due to budget impact concerns. Although physicians believed it to be superior in efficacy, the test was not reimbursed, and they had to contend with different, suboptimal choices unless patients paid privately.

Background analysis

CONTEXT: DEFINING THE PROBLEM

Spending on most therapies will grow at slower rates or even decline through 2015, driven by overall stagnation of new medicine development and a number of medicines moving off patent. Specialty medicines are one of the few areas that will experience continued growth in the medium term due to novel mechanisms, improved efficacy, and relatively large patient populations, leading to increased uptake of high-value medicines.

Specialty medicines include those that treat specific, complex chronic diseases with four or more of the following attributes:

- Initiated only by a specialist.
- Require special handling and administration.
- Unique distribution.
- High cost.
- Warrant intensive patient care.
- Might require reimbursement assistance.

These clinical developments have paved the way for personalised medicine to flourish as an area for both targeted therapies and companion diagnostics, typically technically sophisticated laboratory tests. Figure 28 exemplifies oncology as currently one of the largest areas of spending with a trend likely to continue into 2015.

This is not surprising given that cancer is in the top three drivers of disease burden among high- and middle-income countries, and in the top 10 among low-income countries (WHO 2004 & 2008).

Despite the growth in cancer medicine burden and consumption, policymakers and payers have struggled to find a balance between maintaining medicine access for patients with specific needs and the need to control costs. This is especially the case in Europe, where nationally funded health systems prioritise access to healthcare, including medicines. In response, payers have started to use a variety of tools to control pricing and market access, and shift the risk to manufacturers. These include risk sharing agreements, prescribing guidelines, health technology assessments (HTAs), and regional restrictions.
Genetics and biomarkers indicate variations in patient response to specialty treatment in diseases such as cancer. As a result, the field of personalised medicines is promising for better medicine use from a value and cost perspective. As variations exist within patient populations and as markers can change over the course of a patient’s disease, treatment using a ‘one size fits all’ approach can result in an inefficient use of scarce resources. Personalised medicine offers an opportunity for health systems to avoid the costs of treating patients ineffectively and to improve their quality of life. Personalised medicine results in other economic benefits such as reduction of hospitalisation costs, increasing productivity gains from patients and caregivers as patients’ quality of life improves and they can resume normal lives.

In oncology, this is a pertinent subject given the small number of patients who actually respond to treatment (not surprising given ~450 ‘niche’ diseases and types), resulting in the treatment of many for the benefit of few. In many cases, patients do not respond to treatment or develop severe adverse events that can lead to second primary cancers, cognitive dysfunction, and other adverse events. The following statistics shed light on this:

- On average across all cancers, efficacy with standard treatment is only 25% (Miller et al. 2011).
- Only about 5% of women with oestrogen receptor (ER)-positive breast cancer that has not spread to the axilla require or benefit from cytotoxic chemotherapy (Simon 2010).
- At least 1 in 2 women with node negative, ER-positive breast cancer that receive adjuvant chemotherapy experience early and late adverse events, without a clear subgroup defined with predicted benefit (National Comprehensive Cancer Network 2008).
- Approximately 40% of patients with metastatic colorectal cancer (mCRC) show KRAS mutations that make their cancers unresponsive to one of the leading drugs for its treatment. In fact, treating these patients with this drug can lead to very severe adverse effects because the body is unable to metabolise the drug correctly.

An increasing understanding in the science community about human genetic variation has led to an emergence of tools that detect abnormalities in gene expression. In the scope of this report, these tools focus on predictive testing, one of the best-known examples of personalised medicine and historically pioneered in the oncology space. They include:

- **Breast cancer**: Oncotype DX® shows likelihood of chemotherapy benefit in early stage, node-negative, ER-positive breast cancer. MammaPrint® launched afterwards with a higher price and wider indication, demonstrates competitive market forces.
- **Colorectal cancer**: Dako’s EGFR pharmDx™ test kit or Therascreen® KRAS RGQ PCR Kit detects KRAS gene mutations to determine therapy choice, one of the first examples of predictive testing that deselects patients due to lack of efficacy. Although this tool has been available for years, many providers are still not using it.
Cancers with very recent diagnostic innovations include:

- **Non-small-cell lung cancer (NSCLC):** Vysis ALK Break Apart FISH Probe Kit detects anaplastic lymphoma kinase (ALK) protein fusions to identify patients most likely to benefit from a treatment for NSCLC. The USFDA approved both the treatment and the test in August 2011 (US Food and Drug Administration 2011a, 2011b).

- **Malignant melanomas:** The cobas® 4800 BRAF V600 mutation test detects the BRAFV 600 mutations and identifies appropriate treatment. The USFDA also approved the treatment and companion diagnostic in August 2011 (US Food and Drug Administration 2011c).

USFDA approvals, as noted above for both NSCLC and malignant melanomas, do not specify brand tests so university-based or hospital centres with testing facilities can easily replicate and offer the tests, threatening the intellectual property interests of diagnostic manufacturers post-launch.

Although there have been recent advances using personalised medicines for diseases such as type 2 diabetes, hypertension, etc., they are still in their infancy. As such, these tools are very costly and resource-intensive. Predictive diagnostic analyses for such diseases are out of the scope of this report but this area permeates other diseases as well.

### IMPACT ASSESSMENT

This section is divided into two subsections. First, it highlights the benefits of predictive diagnostics from the perspective of reducing expensive treatments for patients who do not need them. That is, reducing costs by not treating ineligible patients. Second, it covers the benefits of predictive diagnostics by targeting treatments to patients who are likely to benefit.

#### REDUCE COSTS BY NOT TREATING INELIGIBLE PATIENTS

**Breast cancer**

A cost of approximately 95Mn USD per year is avoided by not treating breast cancer patients with chemotherapy when they are unlikely to benefit from the treatment. This is based on 50,000 women who are diagnosed with ER-positive, lymph-node negative breast cancer in the US each year and are eligible for testing with Oncotype DX® (Falkingbridge 2009). IMS Institute research shows that using Oncotype DX® to predict a patient’s benefit from chemotherapy as well as her risk of breast cancer recurrence (thereby identifying how she should be treated) can reduce chemotherapy use by 20% to 35% and avoid costs of approximately 1900 USD per patient tested (PricewaterhouseCoopers 2009).

**Colorectal cancer**

There is evidence that suggests that KRAS diagnostics testing to identify colorectal cancer patients who are unlikely to respond to large-molecule EGF receptor (EGFR) inhibitors could save the US health system 600Mn USD (Miller et al. 2011; Huriez 2011). This diagnostic test was the first in personalised medicines to deselect patients for therapies. In fact, in the US the treatment is not approved for patients with the KRAS mutation, as it is not only ineffective but also harmful.

### INCREASE HEALTH OUTCOMES BY TREATING ELIGIBLE PATIENTS

Evidence also exists that shows how diagnostic tools may, in fact, be cost ‘neutral’ or more costly (Davis et al. 2009). This happens when the cost of the alternative treatment (as a result of the testing) is cost-neutral or more costly than the cost of treating the disease with existing medicines. Higher costs as a result of diagnostics testing also occur when there is a low probability of identifying patients requiring intervention. This is probably the case with the recently USFDA approved companion diagnostics and treatments for non-small-cell lung cancer and malignant melanomas.

**Non-small-cell lung cancer (NSCLC)**

A new treatment was approved in the US for NSCLC patients who express an abnormal ALK protein (Kwak 2010). However, due to the limited number of lung cancer patients who express this protein abnormality (an estimate that varies between 4%-5%), a companion diagnostic was also developed and approved
alongside the treatment (Choi et al. 2010; US Food and Drug Administration 2011a). Given the very small subset of late-stage patients who express the abnormality, a partial and varied response rate to the treatment, and the expense of the treatment and diagnostics test, it would seem reasonable to assume that this specific therapeutic treatment would be more costly to payers.

However, these costs have a potential for great benefits. There is evidence that shows positive benefits of the treatment including tumour shrinkage and disease stability (Kwak 2010). Furthermore, inspiring stories from patients have been noted. Matt Ellefson is a lung cancer survivor on a targeted treatment who has recently completed a half marathon. “When I was first diagnosed, I went looking for another survivor with a similar experience who was now living a normal, happy life, but I couldn’t find one. They had all passed away. So I promised myself that when I was healthy I would be that person for someone else” (Chriscaden 2012).

It remains to be proven whether this is an exception or a rule. Needless to say, the ‘Lazarus effect’ has been witnessed among responders to some medicines (e.g., Tarceva® [erlotinib] and Iressa® [gefitinib]), leading to nine to 12 months of extra life. The long-term impacts and impact on survival have not yet been validated, and there are a number of serious adverse effects from the treatment including liver problems, inflammation in the lungs, nausea, diarrhoea, and vomiting which must also be considered from a health outcomes perspective (US Food and Drug Administration 2011a).

**Malignant melanomas**

The FDA also approved a new treatment for patients with malignant melanoma who express a BRAF mutation. This treatment was approved for use with its companion diagnostic (US Food and Drug Administration, 2011c). Patients with advanced and aggressive malignant melanoma can take the treatment to inhibit the mutated forms of the BRAF protein found in about half of all cases of melanoma.

Given the small population of patients with aggressive skin cancer and the expense of the treatment and diagnostics test, IMS Institute analysis shows that testing all patients and treating half the patients who have the gene mutation would cost the health system more. However, with melanoma, there are limited alternatives. Treating malignant melanoma patients with chemotherapy wastes resources because quality of life is undermined and survival time is not prolonged. Increased costs can result due to increased hospitalisations and severe adverse events.

Instead, Zelboraf® (vemurafenib) is an oral medication that enables patients to return to work, and improve productivity. The approval of the companion diagnostic and therapeutic was made by the FDA based on early positive outcomes from clinical trials that demonstrated a reduction in the growth of cancer and potential improvements in overall survival. To date, the median survival has not yet been reached (+8 months). Adverse effects of the new treatment include severe skin reactions, changes in electrical heart activity, liver problems, eye problems, or new lesions that can be surgically removed (US Food and Drug Administration 2011c).

Under these circumstances, it is becoming increasingly important for payers and policymakers to consider approaches such as health technology assessments to understand the implications of introducing novel diagnostic tools in the health system. Additionally, guidelines for use and appropriate reimbursement policies need to be introduced and adapted.

Figure 29 on the following page, demonstrates cost spending and cost avoidance in populations for which predictive testing and targeted treatments are available.
Non-Small-Cell-Lung Cancer 10% 20% 30% 40% 50% 60% 70%
Breast Cancer 25% 50% 75% 100%
Malignant Melanoma 0% 10% 20% 30% 40% 50% 60% 70%
Colorectal Cancer 50% 100%

Potential for increasing or avoiding costs at a population level

250 USD to test for ALK mutation to select patients who will respond to a targeted treatment (crizotinib) that costs 115,000 USD per year (National Cancer Institute, 2011)

2,500 USD to test for risk of recurrence to select patients who will respond to chemotherapy that costs approximately 51,000 USD per year (Kurlan, 2007)

150 USD to test for BRAF mutation to select patients who will respond to a targeted treatment (vemurafenib) that costs 112,000 USD per year (National Cancer Institute, 2011)

450 USD to test for KRAS mutation to select patients who will respond to treatment with EGFR inhibitor (cetuximab) that costs approx. 61,300 USD per year (Nelson, 2009)

In absolute numbers, there are more breast cancer and colorectal cancer patients, which would result in a greater magnitude of cost avoidance.

Calculations are based on the following assumption: The entire patient population is tested to identify a few for specific treatments when compared to standard of care.


2. RIGHT MEDICINE TO THE RIGHT PATIENT

Minimise supply disruptions: medicine shortages and substandard medicines

*Medicine shortages and substandard medicines are the most critical challenges in supply disruptions related to medicine use.*
2. RIGHT MEDICINE TO THE RIGHT PATIENT: MINIMISE SUPPLY DISRUPTIONS: MEDICINE SHORTAGES AND SUBSTANDARD MEDICINES

Ministerial relevance and recommendations

- **Medicine shortages**
  - Ministers of Health can establish national guidance to ensure continued medicine supply, develop a special committee to manage medicine supply, and/or establish an early warning system for manufacturers to report drug supply fluctuation in advance.

- **Substandard medicines**
  - Substandard medicines, though primarily regarded as a problem of developing countries, are prevalent globally due to the international trading network. However, controversies on the definition of substandard medicines prevented effective development of interventions and related policies on an international level.

  - Ministers of Health can collaborate on a regional or national level to track the medicine supply chain using barcoding systems.

**Basis for recommendations: Interventions and policy options**

**Medicine shortages**

Management on a national level is crucial to prevent or respond effectively to medicine shortages. There are a few different interventions utilised in other countries to consider:

- National policy guidance can ensure continued supply. In November 2011, the UK issued policy guidance in relation to drug supply and trading to ensure continued and sufficient supply for domestic patients (UK Department of Health produced guidelines).

- Special committee or programme dedicated to addressing drug shortages at the national or subnational level (e.g., US FDA Drug Shortages Action Plan within the Center for Drug Evaluation and Research; ASHP (American Society of Health-System Pharmacists), Drug Shortage Resource Center; UK, Pharmaceutical Services Negotiating Committee Drug Shortages Monitoring; other examples exist in Australia and New Zealand).

**RECOMMENDATIONS: MEDICINE SHORTAGES CAN BE ADDRESSED WITH POLICY GUIDANCE, DEDICATED COMMITTEES, AND AN EARLY WARNING SYSTEM**

<table>
<thead>
<tr>
<th>POTENTIAL MOH INTERVENTIONS</th>
<th>REFERENCE POINT</th>
<th>SPEND</th>
<th>HEALTH OUTCOME</th>
<th>TIME SCALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy guidance in relation to drug supply and regulation to ensure notification by suppliers</td>
<td>UK Department of Health, 2011</td>
<td>Moderate cost</td>
<td>Low</td>
<td>3-5 years</td>
</tr>
<tr>
<td>Special committee to assess risk of medicine shortages</td>
<td>US FDA</td>
<td>Moderate cost</td>
<td>Low</td>
<td>3-5 years</td>
</tr>
<tr>
<td>Early warning system with informatics capabilities</td>
<td>SMS for Life (Novartis’ malaria programme); other options are currently being explored in UK, Canada, and the US</td>
<td>Moderate cost</td>
<td>Medium</td>
<td>2-3 years</td>
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RECOMMENDATIONS: SUBSTANDARD MEDICINES* CAN BE ADDRESSED THROUGH INTERNATIONAL COLLABORATION, EDUCATION, INDUSTRY PARTNERSHIPS, A TRACKING SYSTEM, AND A DEDICATED GOVERNMENT UNIT

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<th>POTENTIAL MOH INTERVENTIONS</th>
<th>REFERENCE POINT</th>
<th>SPEND</th>
<th>HEALTH OUTCOME</th>
<th>TIME SCALE</th>
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<tbody>
<tr>
<td>Join an international effort to better track and identify substandard medicine risk</td>
<td>Pharmaceutical Security Institute</td>
<td>Low cost</td>
<td>Low</td>
<td>3-5 years</td>
</tr>
<tr>
<td>Invest in education campaign targeting healthcare professionals and customers to identify</td>
<td>National Drug Information Center, Philippines</td>
<td>Moderate cost</td>
<td>Low</td>
<td>0-2 years</td>
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<td>counterfeits</td>
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<td>Collaborate with industry to identify how to prevent counterfeits locally and develop</td>
<td>Pharmaceutical Securities Institute</td>
<td>Low cost</td>
<td>Medium</td>
<td>3-5 years</td>
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<td>responses with the police and customs services</td>
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<tr>
<td>Invest in local or regional medicine tracking system</td>
<td>Brazil Health Surveillance Agency; Argentina National Medicines, Food and</td>
<td>High cost</td>
<td>Medium</td>
<td>3-5 years</td>
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<td>Medical Technology Authority; Directive EC 2001/83/EC in 2011 to combat</td>
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<td>counterfeit medicines by EU Parliament</td>
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<tr>
<td>Fix responsibility for monitoring and triaging reports from different stakeholders within a</td>
<td>Medicines and Health Regulatory Agency (MHRA) in the UK; Pharmaceutical Crime</td>
<td>Low cost</td>
<td>Low</td>
<td>3-5 years</td>
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<tr>
<td>single unit, with mandated authority to conduct investigations either independently or</td>
<td>Unit in Israel</td>
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<td>with law enforcement partners</td>
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- An early warning system underpinned by strong informatics capabilities. This can be used to conduct risk identification, demand forecasting, use of a volatility index, and predictive modelling to identify risks of shortages, particularly in low-cost generics, and to anticipate shortages of critically important medications at the national and regional levels (IMS Institute for Healthcare Informatics 2011).

- Regulation to ensure early notification by suppliers of potential shortages, as well as convenient and cheaper costs for generic application, faster approval times for generics, and faster review of manufacturing sites (Food and Drug Administration 2012).

*Referring to counterfeits, falsified and spurious medicines
Substandard medicines

Mitigating the negative impact of substandard medicines on medicine use (including recalls) requires an international and national approach involving the public and private sectors. On the international level, the WHO launched the International Medical Products Anti-Counterfeiting Taskforce in 2006. Additionally, there are several other initiatives led by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and UK’s Medicines and Healthcare Products Regulatory Agency (MHRA), one of the few worldwide that has its own unit responsible for conducting criminal investigations (European Federation of Pharmaceutical Industries and Associations 2012; Medicines and Healthcare products Regulatory Agency 2012). The International Chamber of Commerce launched Business Action to Stop Counterfeiting and Piracy (BASCAP) to bring industry and governments together to address drug piracy and counterfeit and substandard/falsified medicines.

On the national level, countries employ multiple strategies to tackle the issue with regulatory, administrative, and communication channels. The Israeli Ministry of Health has recently established a Pharmaceutical Crime Unit with law enforcement authority (Siegal 2010). A regulated system using punitive measures can minimise the incidence of counterfeit/substandard/falsified medicines. For example the UK imposes a 5,000 GBP fine and up to six years’ imprisonment for counterfeit distribution (Medicines and Healthcare products Regulatory Agency 2010). Another regulation measure could be more stringent requirements for manufacturers in their product quality test and control.

Other nationally led examples include:

- Collaboration with the pharmaceutical industry to develop a drug vigilance system to monitor the authenticity of the product, report sources of counterfeit/substandard/falsified medicines, check imported raw material quality, and track contaminated products. Brazil has worked with both international and local manufacturers to develop a tracking and authentication system for substandard medicines. ANVISA, the National Health Surveillance Agency of Brazil, collaborated with Pfizer, Bayer, Sanofi-Aventis, and Nycomed on such a system (Blanco 2010). While the intent was to secure the supply chain from illegal products, implementation has not happened due to concerns expressed by local manufacturers that the timeline to put the tracking system in place was not adequate, and labelling and repackaging costs would be excessive.

- A drug tracking system such as the one implemented in Argentina by the National Medicines, Food and Medical Technology Authority that includes each individual and company involved in the supply chain of a medical product (Food and Drug Administration 2011). In this system, each package-unit is given a unique identifier that includes a batch number and expiration date, allowing the product to be monitored en route from the manufacturer to distributors, logistics operators, pharmacies, healthcare facilities, and patients.

- A drug tracking system that provides a specific square or Quick Response code for medicines to reduce counterfeit/substandard/falsified products. This has been tried in Turkey, for example, with potential learnings for other systems. Research led by the General Directorate of Pharmaceuticals and Pharmacy in Turkey demonstrated the challenges of implementing such a system. Although 65% of pharmacists believe that this system works, nearly all reported the additional burden it placed on their workload. Additionally, 90% reported not receiving training on how to implement such a system. The combination of inadequate training for pharmacists and long processing times for information suggests that these factors are critical for successful implementation of a similar programme in other countries (Yildirim 2011).

- Educational programmes that target wholesalers, healthcare professionals, and consumers to recognise counterfeits and mitigate use of potentially contaminated medicines. For example, the National Drug Information Center in the Philippines developed an educational intervention targeting drug sellers and consumers on the risks of counterfeit, substandard, or falsified products. Their efforts primarily included dissemination of printed brochures and posters as well as training for drug sellers. Results showed increased awareness.
of counterfeit/sub-standard/falsified medicine existence and an interest in inquiring about counterfeit medicines. The greatest impact was on consumers, who were 13% more likely to inspect medicines for counterfeit signs and 32% more likely to receive advice or information from drug sellers (Galang et al. 2011).

Background analysis

Despite challenges with data and evidence, the following discussion sheds light on why medicine shortages and substandard medicines as supply disruptions warrant attention in medicine use analysis.

MEDICINE SHORTAGES

CONTEXT: DEFINING THE PROBLEM

In this context, medicine shortages are considered a form of supply disruptions as they occur when supply is unable to meet therapeutic demands. Supply disruptions prevent patients from obtaining their medication at the right time when suppliers are unable to meet the necessary demand. IMS Institute found that this is not a major challenge in most developed countries. Where it has been a challenge, primarily it has been in certain therapeutic areas and in the hospital setting.

- In the Netherlands, four injectable branded medicines were discontinued in 2002, leading to challenges in quality of care for hospital patients. In some cases, consecutive retraction by suppliers of medication for the same indication is an example of an uncoordinated retraction (Liem et al. 2004). More recently, the Netherlands has experienced shortages in oncology treatments (PR Newswire 2012).
- In Hungary, essential chemotherapy treatment 5FU has been in short supply as of November 2011 due to an increase in demand and manufacturing difficulties (Generics and Biosimilars Initiative 2011).
- The UK has experienced a general shortage of biosimilar versions of granulocyte colony-stimulating factor (G-CSF) used to accelerate patient recovery from neutropenia after chemotherapy. Other medicines in the UK that have experienced shortages are those for kidney disease, high blood pressure, and epilepsy. The Pharmaceutical Services Negotiating Committee (PSNC) in the UK has also reported shortages of Femara® (letrozole), one of the first-line therapies for metastatic breast cancer, and Zyprexa® (olanzapine) for schizophrenia (Donnelly 2011).
- Medicine shortages in the US are highly concentrated on generic injectables affecting major classes such as oncology, antibiotics, and cardiovascular medicines (IMS Institute for Healthcare Informatics 2011). Most of these drug shortages are due to a fluctuating market with a shrinking number of suppliers meeting a growing demand for medicines. In the US, for example, over 50% of medicines in shortage have two or fewer suppliers (Cherici et al. 2011; IMS Institute for Healthcare Informatics 2011; Liem et al. 2004).
- Novartis’ SMS for Life programme exemplifies an innovative public-private partnership approach to monitoring malaria medicine use and eliminate stock-outs. The programme uses a combination of mobile phones, SMS messages and electronic mapping technology to track weekly stock levels at public health facilities which dispense anti-malarial medicines. Health facility workers are rewarded with free airtime for responses via SMS to weekly stock requests. The partnership involves IBM, Medicines for Malaria Venture (MMV), the Swiss Agency for Development and Cooperation (SDC), Vodacom and Vodafone and is under the WHO’s Roll Back Malaria Partnership. In 2009, a six-month pilot programme conducted in three districts in Tanzania covering 1.2 million people demonstrated impressive results: Stock-outs reduced from 79% to less than 26% in all districts. Since then, the programme has been rolled out nation-wide in Tanzania, with support from the Minister of Health. Use of SMS technology through the SMS for Life programme to prevent stock-outs is now expanding to other countries, including Ghana, Kenya and the Democratic Republic of Congo (Novartis Malaria Initiative 2011). This programme is designed to be scalable beyond malaria medicines. Indeed, it has already demonstrated to work for surveillance and monitoring of rapid diagnostic tests (both supply and use), bed nets, antibiotics, leprosy and tuberculosis medicines (World Business Council for Sustainable Development 2012).
**IMPACT ASSESSMENT**

**Economic Burden**

The health system suffers financial loss: For example, approximately 0.02% of total health system expenses could be avoided from minimising drug shortages in the US. These expenses are likely underestimated as drug shortages also cause suboptimal medicine use in the primary care sector. The majority of these costs are due to the additional labour required by pharmacists and technicians to manage drug shortages. Pharmacists and pharmacy technicians spent eight to nine hours per week to manage shortages, resulting in an additional 216Mn USD in labour expenses (Kaakeh et al. 2011). There are also increased costs for substitution therapies. Shortages could cost US hospitals at least 200Mn USD annually through the purchase of more expensive generic or therapeutic substitutes (Alkire 2011). The highest areas of cost are infectious diseases (5% of losses), surgery, oncology, and cardiovascular therapies (Alkire 2011).

**Worse outcomes**

Drug shortages not only result in negative impacts on patient safety and quality of care, but also lead to financial loss to the health system. In terms of care quality, physicians reported worsened clinical outcomes from compromised care due to changes in clinical prescribing without familiarity with alternative treatment options as a consequence of drug shortage (Kaakeh et al. 2011). These may threaten patient safety when alternative drugs fail to work (e.g. some bacteria are insensitive to other available antibiotics). In 2010, the Institute for Safe Medication Practices in the US found more than 1,000 shortage-related errors and adverse patient outcomes, including at least two deaths and several extended hospitalisations (American Society of Health System Pharmacists 2010). These were due to:

- Dosing errors with alternative treatment options.
- Product mix-ups during preparation.
- Delayed treatment due to coding reconfiguration for new medicines.
- Therapy omissions in some cases.

Anti-infectives constitute one of the major drug class shortages in the US, a dangerous situation given the risk of antimicrobial resistance and reduced treatment options.

**SUBSTANDARD MEDICINES**

**CONTEXT: DEFINING THE PROBLEM**

Substandard medicines are also referred to as counterfeit, fake, falsified, or spurious medicines, but the definition has been and continues to be highly contested. WHO definition of counterfeit medicines is the one also used by the Pharmaceutical Security Institute, one of the few international efforts currently in place to track and address counterfeits. Counterfeits are branded and generic medicines that are:

- Deliberately and fraudulently mislabelled with respect to identity and/or source (e.g. not produced by the original manufacturer).
- Contain no active ingredient, incorrect quantities, or an undeclared active ingredient.
- Are contaminated with other materials (chalk, boric acid, lead, and rat poison are typical examples).
- Are past their expiration date.
- Contain no or incorrect patient information leaflets.

WHO also offers a definition for substandard medicines that encompasses counterfeits: “Substandard medicines are products whose composition and ingredients do not meet the correct scientific specifications and which are consequently ineffective and often dangerous to the patient. Substandard products may occur as a result of negligence, human error, insufficient human and financial resources, or counterfeiting. Counterfeit medicines are part of the broader phenomenon of substandard pharmaceuticals. The difference is that they are deliberately and fraudulently mislabelled with respect to identity and/or source” (World Health Organization 2003).

However, concern has been highlighted around the wider definition of ‘counterfeit’ as potentially threatening to generic medicines of assured quality on which many developing
countries depend (Clift 2010). Counterfeiting has become a controversial term given its association to intellectual property in the context of quality, safety, and efficacy of medicines.

Moreover, there are also suggestions by international institutions such as the European Commission for an alternative way to overcome the challenges of defining counterfeit and substandard/falsified medicines: “[Medicines that are] falsified in relation to their identity, history, or source. These products usually contain substandard or falsified ingredients, or no ingredients, or ingredients in the wrong dosage, including active ingredients, thus posing an important threat to public health.” (European Compliance Academy 2011). This definition attempts to isolate the intellectual property issue and in this way differentiate from counterfeits.

Debate continues about whether counterfeiting of medicines should be defined in the context of intellectual property discourse (remit of organisations such as the World Trade Organization) or in the medicines quality discourse (remit of WHO). Some attention to the debate in this research is relevant because it poses a challenge to the very initial step of responsible medicine use, ‘right medicines,’ since regardless of the term there is a risk that patients do not get the (branded or generic) medicine they were supposed to get. In other words, prescribers, pharmacists, and patients agree on the medicine that needs to be provided but forces outside of their control contribute to ‘falsified, spurious, substandard or counterfeit’ medicines entering the supply chain and disrupting medicine use.

According to Chatham House, an independent policy institute in London, failure to identify a common definition hampers international efforts towards a constructive policy debate and action (Clift, 2010). In light of existing debates, this research does not suggest a prescriptive view on the definition and conclusive evidence is not offered on the estimated potential avoidable cost from such medicine use. However, research sheds light on why this issue should not be marginalised in the context of right medicines in this research and offers potential interventions and policy options that policymakers can consider.

### IMPACT ASSESSMENT

In relation to health policy, such medicines pose a risk from a safety and cost perspective. These medicines do not work appropriately in patients and/or delay quality treatment, leading to adverse drug events. In some cases, substandard/counterfeit/falsified medicines could contain substances injurious to life (IFPMA). The cost of recalls to payers and companies is not minimal, though manufacturers bear the burden. Recalls from both substandard and contaminated medicines have increased three-fold from 2008 to 2009 in the US and incur the following avoidable costs (Lehman 2010):

- Avoidable costs on medicines which produce no or adverse clinical effects.
- Additional costs from adverse drug events or death.
- Manufacturers incur high revenue losses from drug recalls in the form of lawsuits and associated logistics.

Although the evidence is limited, substandard/counterfeit/falsified products are a rising global problem across all therapeutic areas and countries. It is worth noting that weak regulation and enforcement in many countries means that most counterfeit medicines and their impact are undetected. Therefore, available data are from countries and/or regions that are effectively tracking counterfeits through law enforcement and inspection by drug regulatory agencies. In middle- and low-income countries, most data are estimated based on the risk level and weak regulation. Even in high-income countries, detecting these medicines is a challenge. There is limited public awareness and it can be very difficult for physicians and/or patients to distinguish between substandard/counterfeit/falsified medicines and real ones.

According to the Pharmaceutical Security Institute (PSI), this challenge (with ‘counterfeits’ used in this context) reaches almost all therapeutic classes, particularly favouring drug classes with higher demand and prices. Most of these medicines are prescription and/or inpatient medicines. The top three
classes with counterfeits are genitourinary (37%), anti-infectives (12%) and central nervous system medicines (12%) (European Federation of Pharmaceutical Industries and Associations 2009). In 2010, the metabolism therapeutic category led the largest percentage increase (+182%) (Chu 2010). Other categories with increases included cytostatic (+20%) and cardiovascular (+5%). Most recently, in January 2012 steroids and medicines for erectile dysfunction topped the list of counterfeited medicines seized by Brazilian authorities between 2007 and 2010, accounting for 66% of all counterfeits (Taylor 2012).

Factors contributing to counterfeiting are multifaceted and include:

- Monetary rewards from the margins between low production costs and high demand and/or prices, making it a very lucrative yet underground business.
- Lack of regulatory deterrence, which indirectly tolerates the act of counterfeiting.
- Easy access for patients to medication through e-commerce, where online pharmacies can sell adulterated products.
- A need for cheaper medicines that influences people to seek sources outside official, regulated supply, primarily in low-income countries where the majority of medicines are paid for out-of-pocket.
References


IMS Institute for Healthcare Informatics. Drug Shortages: A closer look at products, suppliers and volume volatility. 2011


References continued


Nonmedical use and abuse of prescribed and OTC medicines are growing health problems in developing and developed countries.
3. PATIENT USAGE: REDUCE MEDICINE ABUSE

Ministerial relevance and recommendations

- Nonmedical use and abuse of prescribed and OTC medicines are growing health problems in developing and developed countries. Up to 2.7% of the US population are current users of prescription medicines for nonmedical purposes.

- Persons who abuse medicines incur cost primarily on hospital admissions, ED visits, and loss of productivity. Potential benefits can be gained from these costs if medicine abuse can be prevented.

Ministers of Health can support interventions to monitor and prevent medicine abuse by:

- Establishing a medicine abuse warning and reporting system.
- Building a surveillance or alert system to identify potential cases of medicine abuse.
- Providing community and family support, especially for the problem of teenage medicine abuse.

RECOMMENDATIONS FOCUS ON A NATIONAL SURVEILLANCE SYSTEM, EARLY ALERT SYSTEM, TREATMENT GUIDELINES, RESPONSIBLE DISPOSING MECHANISMS, LEGISLATION, AND EDUCATION OF HEALTHCARE PROFESSIONALS

<table>
<thead>
<tr>
<th>POTENTIAL MOH INTERVENTIONS</th>
<th>REFERENCE POINT</th>
<th>SPEND</th>
<th>HEALTH OUTCOME</th>
<th>TIME SCALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Establish a national surveillance system to monitor medicine abuse from self-reporting, ED visits, etc.</td>
<td>New Zealand (IDMS), USA (SAMHSA, DAWN)</td>
<td>Moderate cost</td>
<td>Low</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Implement an alert/warning mechanism for medicines most likely to be abused by patient within a medicines prescription and dispensing surveillance system</td>
<td>Canada (PharmaNet in British Columbia)</td>
<td>Moderate cost</td>
<td>Medium</td>
<td>3-5 years</td>
</tr>
<tr>
<td>Ensure treatment guidelines lead to the cautious and appropriate use of commonly abused medicines</td>
<td>Canada (National Opioid Use Guideline Group)</td>
<td>Moderate cost</td>
<td>Medium</td>
<td>3-5 years</td>
</tr>
<tr>
<td>Establish a programme/process to ensure the responsible disposal of prescription medicines</td>
<td>USA (Community Take-back Programme)</td>
<td>Moderate cost</td>
<td>Low</td>
<td>0-2 years</td>
</tr>
<tr>
<td>Regulate and legislate online sales of medicines</td>
<td>EU Parliament Directive EC 2001/83/EC in 2011 to combat counterfeit medicines</td>
<td>Moderate cost</td>
<td>Medium</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Educate health professionals, pharmacists, and patients on medicine abuse issues and risks</td>
<td>US (SAMHSA and SUPER Family Education programme)</td>
<td>Low cost</td>
<td>Low</td>
<td>2-3 years</td>
</tr>
</tbody>
</table>
Basis for recommendations: Interventions and policy options

1. Early assessment of patients’ likelihood of medicine abuse

Healthcare providers should consider assessing patients’ inclination for medicine abuse at an early stage by investigating their family or personal medical history, or by setting rules at initiation of treatment based on joint consensus. They also need to pay extra attention when prescribing to women, young people, and the elderly, which are vulnerable groups for medicine abuse.

2. National efforts to establish a warning and monitoring system to identify medicine abuse

The US Substance Abuse and Mental Health Service Administration (SAMHSA) was established as the Federal government’s leading agency to target substance abuse (including medicine abuse) and mental health services in American communities. SAMHSA runs a surveillance system, the Drug Abuse Warning Network (DAWN) that monitors drug-related hospital emergency department (ED) visits and drug-related deaths investigated by clinical examiners. Their statistics are useful in the provision of related trend data on adverse events caused by medicine abuse.

The Illicit Drug Monitoring System (IDMS), run by SHORE (The Centre for Social and Health Outcome Research and Evaluation) of New Zealand’s Massey University, provides ongoing information on drug use and drug-related harm in New Zealand, including the use of prescribed medicines such as methylphenidate, morphine, methadone, and benzodiazepines. The IDMS is able to analyse the trend of drug use based on yearly updates of the data.

3. An electronic surveillance system that typically involves data on prescriptions written and medicines dispensed

Australia has reported that surveillance systems are effective at reducing prescription medicine abuse, fraud, and diversion (Drugs and Crime Prevention Committee 2007). The Maryland state government in the US is considering a monitoring system that would require pharmacies to log each filled prescription in a database, allowing prescribers in doctor’s offices, hospital EDs, or urgent care facilities to check before writing prescriptions for the same medications (Cohn 2011).

PharmaNet in British Columbia, Canada, is a province-wide monitoring network that prevents overconsumption of prescription drugs by unintended duplication or fraud as one of its core functions. Various types of information are maintained on PharmaNet, including patient medication histories and demographic profiles, drug information, historical patient claims, and drug interactions. The network links all the provincial pharmacists to a central database so they can access patients’ medical information to collate dispensing and prescribing data and prevent duplication. Medical practitioners are also allowed to request dispensing records for a particular patient.

Australia initiated Project STOP at the national level to prevent the diversion of pseudoephedrine. Upon requesting a pseudoephedrine-based product, pharmacists ask to see an acceptable form of photographic identification and record the patient’s identification card number in a protected database. The database is checked to see if the patient’s identification number was previously entered within an appropriate threshold period. Pharmacists can then decide whether or not to supply the product based on a determination of the patient’s therapeutic needs and database suggestions. Since the Project STOP system went online in 2005, pharmacists have denied sales on 26,000 occasions (FIP - International Pharmaceutical Federation 2012).

4. Guidelines can be developed to inform responsible use of commonly abused medicines, such as opioids

While guidelines can lead to cautious and appropriate use of these medicines, it is important to note that preventing nonmedical use of medicines also must be responsive to the demand of patients who actually need them. Canadian physicians and medical regulators recognised a growing need
for guidance regarding opioid use for chronic noncancer pain. The first National Opioids Guideline was founded on an evidence-based professional review in 2010. The practice recommendations assist physicians to use opioids effectively and safely for chronic noncancer pain. This clinical practice guideline also calls for patients to be informed about the potential benefits and risks of opioids, and instructs doctors to stop prescribing opioids if patients don’t respond to treatment or there is a risk of addiction (Canada: National Opioid Use Guideline Group 2010).

5. Responsible disposal of unused medicines in prevention of being taken for abuse purposes

High-risk, high-value medicines should be dispensed in limited quantity and returned by patients if they are unused. The 2011 US Prescription Drug Abuse Prevention Plan included proper medicine disposal as one of the four major strategies. The Community Take-back Program has been set up to recycle unused medicines in local communities (Office of National Drug Control Policy 2008).

6. Regulations and legislation to supervise medicine supply from the Internet and e-pharmacies

For Internet pharmacies within the country, strict registration and approval processes should be implemented and followed, along with regular inspection. Law enforcement can deter the incidence of illegal dispensing without prescription. For pharmacies outside the country, management is more challenging, though customs surveillance can help to some degree to identify high-risk medicines. In 2003, the US Government Accountability Office estimated that approximately 50% of Internet pharmacies that sell controlled prescription drugs were located outside the US (The National Court Appointed Special Advocate Association 2007). Therefore, regulations need to consider the global scope of online pharmacies. In response to the increasing e-pharmacy challenge, the European Parliament included relevant legislations on online sales of medicines in the more recent Directive EC 2001/83/EC to combat counterfeit medicines (European Compliance Academy 2011).

7. Multifaceted education that targets key stakeholders including physicians, pharmacists, and patients

Education for physicians: Physicians need to be aware of abuse among patients, assess and identify patients at risk for medicine abuse, and prescribe responsibly according to guidelines. Education should also emphasise the importance of professional ethics and put patient safety as a priority. General policies for prevention of prescription forgery by patients could be to write both figures and words in prescriptions and cross out unwritten margins. A tamper-resistant prescription form can be designed for high-risk drugs (United Nations Office of Drugs and Crimes 2011).

Education for the public and patients: The general public can be educated to increase the knowledge of medicine abuse and its risks. SAMHSA in the US disseminates point-of-sale information to consumers who purchase highly abused prescription drugs such as hydrocodone, select sleep aids, and oxycodone. Consumers receive one of three information sheets on abuse prevention when they fill prescriptions for these drugs at pharmacies participating in the programme (SAMHSA 2007). Patients on medication need to be informed of early-stage symptoms for abuse and prevent worsening through self-evaluation and management, or seeking help when needed.

It is reported that the number of teens abusing prescription and OTC medicines has reached record heights. Teens agree that obtaining OTC medicines is easier than obtaining prescription medicines since OTC medicines are accessible at home or in community pharmacies (Partnership for a Drug-Free America 2005). Parents should be educated on the management of home-stocked medicines and on skills to supervise their children’s medication behaviour.

8. Treatment for addiction

Once diagnosed, both behavioural and pharmacological treatment needs to be provided to individuals to resolve dependence or addiction. Depending on the type of medication abused, treatment should target the particular
needs of individuals. SAMHSA recommends treatment facilities that are suitable to patients given their location and addiction type. A supporting environment from family and society is conducive to rehabilitation.

Background analysis

CONTEXT: DEFINING THE PROBLEM

Nonmedical use or abuse of medicines is the intentional use of a medication in a way other than as prescribed, or for the experience or feeling it causes (National Institute on Drug Abuse and US Department of Health and Human Services 2011b; Partnership for a Drug-Free America 2005). This can be dangerous due to intrinsic adverse effects of all medicines, particularly when taken without instruction and management by healthcare professionals.

Commonly abused prescription and OTC medicines have psychoactive effects that lead to physical or psychological dependence, and cause adverse events or even death when used at high doses. Prescription medicines abuse is primarily with opioids, CNS depressants, and stimulants.

- Opioids commonly known to relieve pain include hydrocodone, morphine, codeine, oxycodone, and related medications. Low-dose, long-term intake can lead to physical dependence and addiction, while a large single dose can cause severe respiratory depression and death.

- CNS depressants such as barbiturates and benzodiazepines are often referred to as tranquillisers or sedatives and are used to treat anxiety and sleeping disorders. Withdrawal from high-dose benzodiazepines can cause seizures.

- Stimulants are used to treat attention-deficit hyperactivity disorder (ADHD), narcolepsy, or obesity, but are abused for cognition enhancement or recreation. Stimulants carry the risk of a dangerous increase in blood pressure, which can be worsened when they are combined with other drugs or alcohol (Klein 2010). A 2008 study of 113,104 subjects in the US found rates of past-year nonprescribed stimulant use that ranged from 5% to 9% in grade school- and high school-aged children, and 5% to 35% in college-aged individuals. A systematic review of literature found that 16% to 29% of students claimed using stimulants for diversion and were asked to give, sell, or trade these at least once in their lifetimes (Wilens et al. 2008).

OTC medicines such as certain cough and cold medicines, cough suppressants, sleep aids, and antihistamines can be abused either by consumption at higher doses or when accompanied with other illicit drugs or alcohol. Cough syrups and cold medicines are the most commonly abused OTC medications (National Institute on Drug Abuse and US Department of Health and Human Services 2011b). When taken for their psychoactive properties, these OTCs can cause confusion, psychosis, coma, and even death.

Nonmedical use of medicines is a growing health problem for both developed and developing countries. Although it affects only a small proportion of the population, the negative consequences could involve deaths, costs to the health system (hospital admissions), and societal loss (i.e. productivity loss, criminal justice).

- Up to seven million people in the US (2.7% of the population) reported past-month use of prescription drugs for nonmedical use in 2010 (National Institute on Drug Abuse and US Department of Health and Human Services 2011a; National Institute on Drug Abuse and US Department of Health and Human Services 2011b). SAMHSA estimated 52 million people (20% of those aged 12 and older) have used prescription medicines for nonmedical reasons at least once in their lifetimes (Klein 2010). Data relating to OTC abuse in the US has been reported by the annual National Survey on Drug Use and Health (NSDUH). In 2006, around 3.1 million people aged 12 to 25 stated having taken OTC cough and cold medicines for nonmedical purposes (Klein 2010; Office of National Drug Control Policy 2008). OTC cough and cold medicine abuse was found to be most prevalent among teens. In the period from 2006-2007, 4% of 8th graders, 5% of 10th graders, and 6% of 12th graders abused OTC cough and cold remedies (Office of National Drug Control Policy 2008).
In 2009, 0.6% of Canadians aged 15 years and older reported having used a recreational psychoactive pharmaceutical during the past year. The use of prescription opioids recreationally (0.4% annual prevalence) overshadows the use of heroin (0.3% annual prevalence) (United Nations Office of Drugs and Crimes 2011).

Northern Ireland reported the highest annual prevalence of prescription opioids anywhere in the world at 8.4%. The annual prevalence of sedatives and tranquilisers was reported at 9.2%, and antidepressants at 9.1% in the general population (United Nations Office of Drugs and Crimes 2011). According to a survey of 197 GPs in 2011, over half of the frontline GPs who responded are “quite or very worried” about the abuse of prescription medicines in their area (Family Doctor Association 2011).

In South America, more countries report the use of opioids than heroin. Nonmedical use accounts for the majority of opioid use, the highest prevalence being reported in Costa Rica (2.8%). The annual prevalence for prescription opiates in Brazil is reported at 0.5%, while the annual prevalence of benzodiazepines is 2.1% (United Nations Office of Drugs and Crimes 2011).

As OTC medicines are directly dispensed by pharmacies, some studies explored pharmacists’ perception on OTC abuse to estimate the extent of the problem. A study in Jordan found that 94.1% of pharmacists suspected some abuse or misuse of OTC products, and an average of 18.6 regular customers were estimated to be medicine ‘abusers’ in a period of three months (Absoul-Younes et al. 2010).

In South Africa, data from treatment centres showed that cases of drug abuse were related to (benzodiazepenes) (46.4%) and analgesics (44.8%), indicating that the nonmedical use of medicines is a problem (Myers et al. 2003).

However, existing evidence provides insufficient coverage to gauge the real scale of problem due to lack of comprehensive data collection (United Nations Office of Drugs and Crimes 2011). Current sources include reporting of perceived abuse on the pharmacy level, hospital admissions and ED visits, self-reported abuse (in the US), or reporting from members of the public. These methods cannot provide exhaustive estimation on incidence of medicine abuse. Prescribed medicines are provided by doctors and dispensed through legitimate channels to treat medical conditions, while OTC medicines are easily accessible to the public directly. In fact, it is difficult to identify whether those who are taking these medicines are doing so for medical use or not, and if the drugs are taken at excessive doses.

Medicine abuse is driven by a variety of reasons, including internal (personal) factors, external (environmental) factors, or a combination of both, including:

- Varied patient motivations: The underlying reasons from patients include: to recover from medical conditions (pain, sleeping problems, or anxiety); to intentionally alter consciousness (for ritual or spiritual purposes); to enhance performance; or for recreation.
- Increased environmental availability of prescribed or OTC medicines:

  **Increased prescriptions written by physicians:** In the US, between 1991-2010 prescriptions for stimulants increased from five million to nearly 45 million and for opioid analgesics from 75.5 million to 209.5 million (National Institute on Drug Abuse 2011; United Nations Office of Drugs and Crimes 2011). Boath et al found that during 1994-1997 in the UK, prescriptions for proton pump inhibitors (PPIs) had increased by 456%, despite no evidence of increased morbidity for gastrointestinal conditions (Boath and Blenkinsopp 1997).

  **Direct-to-consumer (DTC) marketing promotion:** DTC advertising targets consumers directly and provides medicine information through TV, radio, newspapers, and magazines. This information can be useful when patients discuss their treatment with doctors. However, while evidence suggests that DTC advertising helps prevent underuse of medicines, it promotes overuse as well (Donohue et al. 2007). Influenced by advertisements, patients prompt doctors to provide care.
Medicines for abuse can be obtained through friends and relatives, prescription shopping and/or online pharmacies.

by prescribing. To date, only the US and New Zealand allow DTC marketing.

**Availability of Internet sales:** The purchase of medicines online is often associated with nonmedical use of medicines. One Internet search study from 2003 found that 53% of websites generated by a Google search for ‘no prescription codeine’ offered opiate medications without a prescription. Of these sites, 35% offered depressants (e.g. barbiturates, benzodiazepines) and stimulants for sale as well (Jena et al. 2011).

**Patients’ misperception on the risk of medicines and over-trust of medications:** The general public has shown social acceptance on medicines use (Volkow 2008). Because medicines are provided by health professionals and are suggested to improve health, many people assume that medicines are safe to take under any circumstances, which is not the case. Among US teens, nearly one-third (31%) believe there is nothing wrong with using prescription medicines without a prescription once in a while (Office of National Drug Control Policy 2008).

**Lack of health professionals’ surveillance:** Physicians, pharmacists, and other health professionals who have access to controlled pharmaceuticals can unintentionally contribute to the problem of medicine abuse by not prescribing responsibly, not supervising prescription pads well (patients can then forge prescriptions), or by lacking the ability to identify medicine abuse, though they should not be blamed as a whole. In a large study of patients being treated for substance abuse, 45% reported that their primary physicians were unaware of their abuse (Jena et al. 2011). During medical school training physicians often receive little or no instruction on how to identify the diversion of prescription medicines (Bollinger et al. 2005).

Medicines for abuse can be obtained in various ways. They can be from:

- **Friends, relatives, and colleagues:** In a survey exploring the source of pain relievers for nonmedical use in the US, people obtained prescription medicines from peers, friends, or family members in 56% of the cases (Office of National Drug Control Policy 2008).

- **Prescription shopping:** Prescription shopping typically involves an individual visiting various doctors complaining about the same symptoms to obtain a prescription, or obtaining multiple prescriptions from one doctor. It was reported that individuals might collect thousands of pills during a one-year period and sell them on the street (Kraman 2004).

- **Online pharmacies:** Evidence from local and national samples of prescription medicine abusers suggests that between 1% and 11% of these individuals had purchased controlled prescription medications over the Internet (Jena et al. 2011).

Certain population groups are more vulnerable to medicine abuse, including patients on commonly abused medicines, young people, the elderly, women, and healthcare professionals.

**Patients on commonly abused medicines:** Patients who have been prescribed medicines to treat medical conditions are at higher risk of taking medicines for nonmedical purposes because they have ready access. Individuals who report ADHD symptoms are at highest risk of misusing and diverting stimulants (Wilens et al. 2008). Further risks may arise if a patient has personal or family history of substance use disorder (Edlund et al. 2010).

**Young people:** Among teenagers, the problem of prescription drug abuse is worrisome. Evidence in the US from 2008-2009 demonstrated that after marijuana use, prescription and OTC medicines accounted for most of the commonly abused drugs among 12th graders (National Institute on Drug Abuse and US Department of Health and Human Services 2011a). According to data published by the
Partnership for a Drug-Free America in 2006, 19% of children aged 12 to 17 reported having abused prescription drugs, primarily pain relievers (Manchikanti 2006). College students may take stimulants without a medical need or prescription to improve their concentration, stay awake for long periods, or improve their academic performance (Absoul-Younes et al. 2010; Manchikanti 2006; Swanson and Volkow 2009).

Elderly patients: Older patients are more likely to be prescribed multiple medications long-term, which may lead to unintentional misuse and abuse. Because of their slower metabolism rate, the elderly can get addicted or suffer from serious adverse effects at a lower dose than younger patients (Johns Hopkins Health Alerts 2010; United Nations Office of Drugs and Crimes 2011).

Women: Research has shown that women are more likely to abuse medicines than men due to their combined vulnerabilities (United Nations Office of Drugs and Crimes 2011). Women who are more likely to suffer from anxiety, sleeping disorders, and depression, tend to use medicines to cope with these conditions (Manchikanti 2006).

Health professionals: Health professionals might abuse medicines due to access. It was reported that nurses have been found to be more likely to use prescription drugs for nonmedical purposes (Manchikanti 2006; United Nations Office of Drugs and Crimes 2011).

IMPACT ASSESSMENT

Apart from pharmaceutical costs on nonmedical use, the consequence of medicine abuse is also related to increased treatment admissions (including ED visits), overdose deaths, and related societal cost (e.g. productivity loss and crime) (National Institute on Drug Abuse and US Department of Health and Human Services 2012; United Nations Office of Drugs and Crimes 2011).

In 2001, prescription drug abuse and misuse were estimated to impose approximately 100Bn USD annually in healthcare costs (Kraman 2004). In 2001, an estimate of the cost of prescription opioid analgesic abuse in the US was 8.6Bn USD. Of this amount, 2.6Bn USD were healthcare costs, 1.4Bn USD were criminal justice costs, and 4.6Bn USD were workplace costs (Birnbaum et al. 2006).

Hospital admissions and ED visits: In Canada, data on admissions to the Centre for Mental Health and Addiction demonstrated a significant growth in the number of admissions for dependence on oxycodone, from 3.8% in 2000 to 55.4% in 2004 (Sproule et al. 2009). In 2009, the DAWN system in the US estimated that about 2.1 million ED visits resulted from medical emergencies involving drug misuse or abuse, the equivalent of 674.4 ED visits per year per 100,000 people. From 2004 to 2009, increases were seen in ED visits involving nonmedical use of pharmaceuticals with no other drug involvement (117%), representing about a quarter of all drug-related ED visits and over half of ED visits for drug abuse or misuse. Pain relievers were the most common type of drugs reported in the nonmedical use category of ED visits (47.8%). Hospitalisations in Australia due to poisoning from opioids other than heroin increased over twofold from 1999 to 2008 (Silverside and Dobbin 2010).

Deaths from medicines abuse: From 1980 to 2010, the mortality from unintentional drug overdose has increased 9 fold in the US (1 per 100,000 deaths to 9 every 100,000 deaths). In 2007, the number of deaths caused by drug overdose that involved prescription opioids was higher than for heroin and cocaine combined (CDC Morbidity and Mortality Weekly Report 2012; Silverside and Dobbin 2010).

Societal costs: Medicine abuse also induces loss of productivity in the work place. Those who are dependent on drugs usually suffer from physical and psychological disorders. In addition, medicine abuse is often associated with crimes. Illegal online pharmacies, prescription shopping, pharmacy thefts, and prescription forgeries are partially created by the demand from the abuse of medicines.
References


Boath, E.H. and Blenkinsopp, A. 1997. The rise and rise of proton pump inhibitor drugs: patients’ perspectives. Social Science & Medicine, 45, (10) 1571-1579


FIP - International Pharmaceutical Federation. Report on pharmacists’ organisations’ and pharmacists’ activities-Project STOP. 2012


3. REDUCE MEDICINE ABUSE

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References continued


VI. Capability focus on the role of health informatics

Ministerial relevance and recommendations

Harnessing the power of information can prioritise interventions, monitor progress via process and health outcomes indicators, and support behavior change among healthcare stakeholders and patients.
VI. CAPABILITY FOCUS ON THE ROLE OF HEALTH INFORMATICS

Ministerial relevance and recommendations

• Robust systems of data collection and analysis, commonly referred to as health informatics, are indispensable capabilities for any health system attempting to increase responsible use of medicines.

• Without measuring both process outcomes (such as errors and medicine consumption) as well as health outcomes, health system leaders are unable to identify areas for improvement or prioritise interventions.

• Health informatics provides insights on health outcomes from better medicine use, as well as cost impact outside the medicines budget in higher-cost domains such as hospitalisations.

• When applied strategically, health informatics can inform a variety of policy questions that go beyond medicine use including:

  • Research and development (R&D): How can the government incentivise the biopharmaceutical industry to invest in relevant R & D efforts linked to areas of greatest benefit and improve clinical trial processes?

  • Real-world medicine use: How can informatics inform pricing, reimbursement, and market access decisions? Can informatics also inform medicine management and pharmacovigilance?

  • Patient safety: How can informatics track avoidable adverse events from medication errors, nonadherence, mismanaged polypharmacy, etc., and inform what can be done about these?

  • Advanced technology platforms for this are not always necessary or useful. There are various low-resource-intensive ways to collect information for decision making.

• Health informatics capabilities will only deliver their full value when accompanied by efforts to drive behaviour change among stakeholders based on information.

Silos between medicine and nonmedicine budgets remain a challenge when assessing the impact of medicine use. Better medicine use delays expensive hospital care in the long term but this impact is not systematically tracked because of fragmented budgets and monitoring systems. Real-world evidence from ‘live’ data collection and monitoring has the potential to minimise existing silos and integrate data for different policy decision-making purposes.

While all aforementioned policy questions are relevant to Ministers, the focus in this section is related to the third, with attention to the application of health informatics for decision making in medicine use. Decision making occurs at every point along the patient’s journey and touches different stakeholders, from the physician determining which medication to prescribe to the pharmacist dispensing, and the eventual monitoring and readjustment of the patient’s regimen. As a result, countries and healthcare systems should ensure that comprehensive data collection systems that track prescribing, dispensing and adherence patterns are developed.

The following section describes the relevance of health informatics to responsible medicine use with a focus on the six primary levers for change: Nonadherence, untimely medicine use, antibiotic misuse/overuse, medication errors, mismanaged polypharmacy, and suboptimal generic use. This section covers the relevance of informatics to decision making in each issue, the types of data one might collect, and the informatics systems that can be applied. This section ends with an overview of challenges to building effective health informatics: patient privacy, decisions between centralised and fragmented systems, and data interoperability. A case study from the Minhang District Local Health Bureau in Shanghai, China demonstrates how a government can track real-world evidence to inform policy decisions. This section concludes with a starting list of questions that can be used to strengthen or begin application of health informatics to support the responsible use of medicines.
APPLYING HEALTH INFORMATICS TO INFORM DECISION MAKING ON RESPONSIBLE MEDICINE USE

Nonadherence

Relevance: Data on levels of patient usage (e.g., adherence) are essential to improving physician prescribing decisions to ensure appropriate use. Prescribers and pharmacists can effectively risk stratify patients to ensure interventions are aimed at patients based on their likelihood of being adherent or not, and further segment based on the reason for nonadherence (e.g., adverse effects, relationship with physicians, etc).

Policymakers and payers can use adherence data to guide and inform high-level treatment management decisions and break down conventional thinking. For example, a randomised-controlled trial demonstrated asthma patients prefer inhaled corticosteroids (ICS) over oral leukotriene modifiers (LM). However, US claims data of an insurer by HealthCore, a data analytics company in the US, demonstrated asthma patients on LMs had higher adherence, days on therapy, and reduced likelihood of inpatient admissions compared with patients on ICS. Consequently, the insurer kept preferred-tier status for LM and removed the prior authorisation requirement (WellPoint, Inc. 2008).

Types of data needed: Drug regimens, patient medical and prescribing history, and medication pickups and refills/renewals.

Informatics systems: Systems that monitor patient behaviour remotely are essential to interventions. Systems are most effective when they can integrate information from the pharmacist and provider. While EHRs may be preferable for this, they are expensive and most health care systems encounter fragmentation that has, to this point, rendered this impossible or extremely difficult to implement.

However, mobile health and other technology-related interventions are a low-resource alternative with very high potential to address adherence challenges.

E-prescribing systems: A recent study of more than 40 million prescriptions found that prescriptions that were submitted by physicians electronically were 10% more likely to be filled and picked up by patients (InformationWeek 2012). According to another meta-analysis, between 22% and 28% of paper prescriptions never even make it to the pharmacy, negatively affecting patient adherence (Fischer et al. 2010). A number of other studies have found that electronic prescribing systems also are often associated with useful patient reminders from pharmacists and physicians that serve to increase overall adherence rates (Bell and Friedman 2005).

Mobile health (m-health): Integrated electronic health systems with mobile technology offer timely reminders when patients are overdue for a disease screening, procedure, or medication renewal. From the provider perspective, such systems alert a provider (most often, an individual’s primary care provider) when a patient is either overdue for a test or procedure or has failed to renew their medications in a timely fashion. This is a real-time indicator to physicians of their patients’ adherence levels and allows the physician to structure targeted interventions aimed at increasing adherence among groups that have particularly low levels of adherence (education, one-on-one conversations, etc.).

Mobile technology enables prescribers and pharmacists to directly engage with the patient on a real-time basis as reminders and to identify necessary adjustments. A number of providers have begun to look towards various m-health applications. For example, in a number of studies, text message reminders have been shown to improve adherence rates of regimens for diabetes, HIV/AIDS, and asthma, among others (Pop-Eleches et al. 2011; Strandbygaard, et al. 2010).

Other systems include Medication Event Monitoring Systems (MEMS), which are bottle caps for medication containers with special computer microchips. These microchips store date and time data each time the containers are opened or closed. They are transmitted to healthcare professionals for review to inform interventions.
Untimely medicine use

Relevance: With an increasing NCD burden consisting of asymptomatic conditions, many patients are unnoticed in the health system. Monitoring patients in the primary care setting for specific risk factors can help alert healthcare professionals to the need for intervention. In many cases, medicine use earlier in the disease course can delay complications.

Types of data: High blood pressure, glucose levels, and infections (particularly common among certain subpopulations).

Informatics systems: A critical factor of any health informatics system is coordination between care settings. High costs and worse outcomes occur in the hospital inpatient and/or outpatient setting when patients are not treated in a timely manner within the primary and/or community setting. Information systems can help ensure timely medicine use to prevent or delay hospitalisations. For example, diabetes registries inform which types of patients need to be treated, whether with oral medications or more expensive insulins. They can also be relatively simple. For example, different healthcare professionals can meet regularly to discuss ‘at risk’ patients (e.g., those with ED visits and hospital readmissions) by engaging primary, secondary, and community-based professionals. An e-health system may help ensure patient information consistency across different stakeholders caring for patients, but communication and coordination are equally crucial.

Antibiotic misuse/overuse

Relevance: Currently, the link between total consumption of antibiotics and antimicrobial resistance is poorly understood and consumption has become a commonly used proxy as a specific target. However, less antibiotic use is not necessarily conducive to reducing resistance, and if not monitored carefully can even worsen outcomes and increase resistance. Conversely, the opposite is also true – overuse of antibiotics has been shown to contribute to resistance.

Types of data: Dose, diagnosis codes, frequency of use, duration of treatment, route of administration, and levels of consumption are all critical data points.

Informatics systems: National and international surveillance systems that monitor AMR enable a government to respond to particular outbreaks and quarantine those outbreaks. These systems have become increasingly sophisticated in the US and Europe, which might serve as models for other countries hoping to track AMR. Additionally, countries need to track antibiotic consumption data to monitor the impact of programmes intended to reduce overuse of antibiotics. In the EU, for example, the ESAC project has had a major role in helping to better understand patterns of antimicrobial resistance and consumption. Rooted in cooperation between regulatory agencies, scientific authorities, health insurers, and professional medical organisations across a number of European countries, ESAC provides an important model for how countries can cooperate to track AMR across borders.

Medication errors

Relevance: Information on the number and type of medication errors in both inpatient and outpatient settings is important to identify appropriate interventions. Such information would enable payers, physicians, and pharmacists to target and work with particular hospitals, wards, or prescribers (in the case of pharmacists) who have demonstrated a likelihood of error. For example, a strong system of error reporting at the University of North Carolina Hospital in the US enabled physicians to create a targeted intervention aimed at reducing ARV-related hospital errors among HIV patients, one of the hospital’s dominant sources of error (See US ARV Alert System case study in the medication errors section of this report).

Types of data: While individual hospitals and health systems devote attention to collecting medication errors data, most countries do not have robust data on total numbers of medication errors, type of error, and point in the clinical pathway where the error occurred (prescribing, transcribing, dispensing, administering). Data collection can be prioritised where errors are most likely to happen (administration and prescribing based...
on existing hospital data). Pharmacists can also systematically track correction of prescribing errors. Most countries have created systems for the reporting of this data, but must work to create a climate and culture conducive to reporting.

**Informatics systems:** CPOE systems reduce medication errors associated with prescribing and administration (Kaushal et al. 2003; Kawamoto et al. 2005). Computerised systems can prompt physicians to prevent errors in dosing and wrong medicine administration, while ensuring that patients are not provided medicines to which they have known allergies. Basic CPOE systems can engage in “drug-allergy checking, basic dosing guidance, formulary decision support, duplicate therapy checking, and drug–drug interaction checking” while more advanced systems provide for “dosing support for renal insufficiency and geriatric patients, guidance for medication-related laboratory testing, drug-pregnancy checking, and drug-disease contraindication checking.” (Kuperman et al. 2007). There is strong evidence that barcoding systems, often implemented alongside EHRs, can also reduce both dispensing and administration errors (Cochran et al. 2007; Poon et al. 2006).

**E-prescribing systems** have generated substantial advances in reducing the number of medication errors attributed to the transcription of physicians’ orders. Medication errors in the pharmacy during transcription often occur because a provider’s handwriting is illegible and the pharmacist subsequently provides an inappropriate dose to the patient. The most common error in this setting is a dosing error. Systematic analyses show that e-prescribing systems can reduce the overall percentage of medication errors due to transcription by between 30% and 84% (Ammenwerth et al. 2008).

**Mismanaged polypharmacy**

**Relevance:** Evidence in this research demonstrates that polypharmacy increases with the number of morbidities and patients’ age. There are specific characteristics that are traceable and reveal the likelihood of costly adverse events (such as patient’s age, comorbidities, and medicine consumption). Understanding the prevalence of polypharmacy and the extent (e.g., more than five or more than 20 medicines per patient) can inform the interventions prescribers and pharmacists use to manage patient-level polypharmacy and track related outcomes.

**Types of data:** Data on the individual patient and their medication regimens is important for informing interventions aimed at certain demographic groups and diseases. Useful data include information about the patient (age, gender, medical history), the number of products a patient is taking at any one time, the number of diagnoses the patient has at any one time, and the patient’s ‘status’ (i.e., risk factors that might lead to certain drug-drug interactions). For example, interventions aimed to encourage greater medication review prior to prescribing will be more effective when targeted at more acutely affected groups (e.g., the elderly with multiple medications).

**Informatics systems:** EHRs and the associated decision-support systems are not typically used as tools to combat polypharmacy in clinical settings. However, several studies have shown that countries and health systems have effectively used health data from EHRs to assess the problem of polypharmacy and to better understand the coordination of care between different providers in the healthcare system (Bodenheimer, 2008; Buck et al. 2009). Integrated EHRs may offer the possibility of greater coordination between inpatient providers, GP’s, and various specialists to ensure that the negative effects associated with polypharmacy can be mitigated or even eliminated (Bodenheimer 2008; Schnipper et al. 2008). They may also be used to identify patients most at risk for an AE as a result of polypharmacy, and to structure interventions to target those individuals by way of their primary care physician (Weber et al. 2008).

E-prescribing also presents the opportunity to prevent negative drug-drug interactions. With patients taking many medications, the risk of a negative interaction increases. E-prescribing systems can prevent this interaction by alerting either the prescribing physician or dispensing pharmacist of an allergy or potential interaction.

Finally, countries should look at already existing and perhaps more easily accessible sources of data to drive potential interventions. The Health Alliance Plan in Detroit, Michigan, for
example, used pharmacy claims to identify patients taking between eight and 20 medications and those taking more than 20 medications. They then initiated a pharmacist-led medication management intervention that targeted these patients in order to educate them about their regimens, answer questions, and monitor adherence levels (See the HAP case study in the mismanaged polypharmacy section of this report).

**Suboptimal generic use**

**Relevance:** Macro-level data on medicine utilisation allow policymakers to adjust their pricing and generics procurement policies in response to prescribing and dispensing behaviours. On a micro-level, utilisation data enables hospital or health system administrators to see the specific therapy areas where generic utilisation could be appropriate and higher. They can also undertake appropriate interventions targeting pharmacists and/or prescribers accordingly.

**Types of data:** Drug utilisation trends, drug source (retail, hospital), and pricing (eg., manufacturer prices, discounts, mark-ups along the supply chain where possible and appropriate). Data should also be collected with regard to patient diagnosis and related health characteristics to inform why similar patients are prescribed different medication regimens and decrease relevant prescribing variability.

**Informatics systems:** Though the primary intersection of using low-cost generics and health IT occurs at the level of drug utilisation data collection, other proposals have been introduced to increase the uptake of generics in appropriate circumstances. A number of hospitals in the UK, for example, have introduced a computerised mechanism for International Nonproprietary Names (INN) prescribing. In this system, the prescribing physician enters a brand name drug in a computer, which then changes the name to the INN, and the authority to dispense the brand name drug or the generic rests with the pharmacist. In Germany, physicians use a traffic light system to show how freely a medication should be prescribed. This system is tied to the prescribing quota, which refers to generics and products with discount contracts (See the UK and Germany case studies in the suboptimal generic use section of this report).

**Additional considerations**

**Privacy concerns**

As countries increasingly collect large amounts of data about patients, their medication regimens, their adherence levels, and other behaviours, and potentially even genetic information, health system leaders must think critically about how best to preserve patient privacy and the right to confidentiality. Data is often meant to be used by different healthcare stakeholders for different purposes. For example, physicians and pharmacists would like to know if patients have a mental health-related comorbidity to provide an appropriate medication management process and minimise the probability of nonadherence. In another scenario, employers and/or insurers may discriminate against patients with mental health problems by limiting benefits and/or increasing fees (Noe 1997). An argument can be made that all parties may need to have this kind of patient information for different purposes. Presumably, this is well-intentioned, yet patient privacy is violated when information is misused.

There are legal and technical ways to address privacy concerns although there is no panacea. Laws passed in the US, the EU, Canada, Australia, and Japan have all sought to ensure that patients have the right to decide whether information collected about them can be disclosed to a third party, even for the purposes of academic or policy analysis (Agrawal et al. 2007). Some have even proposed that where data collection mechanisms exist, patients should be required to ‘opt-in’ in order to ensure that countries or healthcare systems do not simply collect data from ill-informed patients (Ray and Wimalasiri 2006). Data can also be protected through technical interventions. For example, patient data can be anonymised and trusted third parties can still access data for policy interventions. The UK’s NHS has often employed this strategy, aggregating patient-level data through the use of unique patient IDs that cannot be traced back to a patient’s actual identity.

**Centralisation and fragmentation**

The way in which data is collected will vary across countries and depend on a number of factors including the type of
While centralised methods of data collection should theoretically provide a simpler mechanism for collecting and aggregating data, they have not experienced very much empirical success. However, no single type of collection system is guaranteed success. While centralised methods of data collection should theoretically provide a simpler mechanism for collecting and aggregating data, they have not experienced very much empirical success. In 2002, for example, the UK invested 12.7Bn GBP in a centralised system of data collection but today still does not have a comprehensive system with interoperable electronic healthcare records across care settings (Morrison et al. 2011; Robertson et al. 2010; Sheikh et al. 2011). A number of challenges confronted the implementation of this system, including the vast scale of England-wide deployments, problems arising from centrally negotiated, long-term contracts, and diversity of multistakeholder interests. Consequently, localised approaches have emerged with a focus on secondary care data collection.

Fragmented efforts that do not necessarily link data sources and span both public and private settings (payer and provider) can provide useful information for policymakers. Examples from the US demonstrate this. In 2008, the FDA launched the Sentinel Initiative to track reports of adverse events from medicines and medical device use. The system recognises the challenges with a centralised approach through data aggregation, and harnesses data available through multiple sources. These sources include EHRs, administrative and insurance claims databases, and registries. The programme has been rolled out as a pilot initially over two years, and the FDA continues to strengthen data collection efforts. It has met the patient data access goal of 25 million people by July 2010 and has been developing partnerships with various data partners to achieve a goal of 100 million people by July 2012 (US Food and Drug Administration 2010).

The National Bioterrorism Syndromic Surveillance Demonstration Program (NDP) in the US is another example of a fragmented system leveraging various data sources. In this model, healthcare providers in the US obtain unique software that is supported by NDP to hold the personal health records of patients. Only aggregated count data is transferred to a central data centre for statistical processing and analysis. Lazarus et al. describe such as a system as a distributed processing surveillance system that supports aggregate data collection and analysis without relying on one central location as the primary data source (Lazarus et al. 2006). Drawbacks to this kind of system include the technical challenge of maintaining distributed software, detecting and reporting errors related to input data, and the need to specify syndromes, age groups, and other data aggregation parameters in advance (Lazarus et al. 2006). Nevertheless, such challenges can technically be overcome and other countries may learn from this viable alternative.

Currently, many high-income country systems have a combination of both an EHR system that gathers data in one or more care settings (e.g., between hospitals, GPs, and/or pharmacists) as well as other data application from third-party sources. Countries such as the UK are heralding widespread use of smartphones and smartphone-based applications to revolutionise the NHS for patients, particularly those with chronic conditions and high blood pressure (UK Department of Health 2012).

Data interoperability

Regardless of the mechanism by which relevant data is combined for decision making (e.g., centralised or fragmented), data interoperability between sources can be a challenge. According to the Healthcare Information and Management Systems Society (HIMMS), data interoperability is “the ability of health information systems to work together within and across organisational boundaries in order to advance the effective delivery of healthcare for individuals and communities.” (Healthcare Information and Management Systems Society 2005). Differences in technical requirements, computer languages (e.g., codes), mandatory and optional requirements, and compliance across technology platforms as well as devices are challenges to a health system attempting to link different kinds of data.

Some efforts are underway to address this, and international collaboration has helped. For example, Continua Health Alliance is a membership-based, nonprofit organisation that addresses this challenge two ways. First, they establish guidelines for combining and applying existing standards to...
patient-connected health products and services (e.g., inhalers, glucose monitors, etc). Second, devices that follow Continua guidelines are then ‘branded’ and flagged as interoperable with other devices. This approach emphasises the use of interoperable telehealth devices that are focused on the individual patient. This more patient-centred approach is less resource intensive and assists providers to make real-time decisions to help individual patients.

As a case in point, Singapore joined Continua and recognised Continua as the preferred method for personal health device connection to the national health record system. The Japanese government is using Continua to manage patient metabolic syndrome through a national programme on obesity. The largest deployment of Continua was for the US Veterans Administration Health System, which used Continua for its chronic disease population with a focus on diabetes, heart failure, hypertension, COPD, and asthma. Existing results are compelling: 53% to 85% of savings in treatment practice and care management can be achieved by using information from Continua-supported products to capture nonadherence and track health outcomes (Kirwan 2012).

Country case study: China

In a study from Shanghai, China, the Minhang District Local Health Bureau implemented a centralised health informatics system that covers all the community care centres and hospitals for local residents, 12% of which are elderly people over the age of 60 (out of a 2.4 million population). The district achieved great improvement in chronic disease management within two years of plan implementation across hypertension, diabetes, and cancer. To do this, the regional bureau set up a web-based cloud computing centre where all EHR and m-health records data is stored and shared by all hospitals and care centres in the region.
Shanghai Minhang District improved chronic disease management with an integrated IT system

BACKGROUND

Since 1999 when electronic health insurance cards were introduced to Shanghai, hospitals and regional healthcare bureaus started to consider applying fully-integrated health information technologies. The Health Bureau in Minhang District was the first regional governmental body in Shanghai to build a region-wide, full-scale, interoperable information platform that links primary care, secondary care, and regional and municipal health bureaus. Minhang District is in the centre of Shanghai, covering an area of 372 square kilometers. The population is 2,429,400, of which 12% are elderly over the age of 60. In 2007, the Minhang District Health Bureau carried out a plan to manage chronic disease with an e-health system.

INTERVENTIONS

The regional health bureau set up a web-based cloud computing centre where all the e-HR and e-MR data are stored and shared by all hospitals and care centres in the region. Every resident carries a health record card that stores their e-HR and e-MR data and is accessible in any hospital in the region. The health card stores residents’ basic health information (weight, height, temperature, pulse, blood pressure, glucose level, living habits, vaccination, medication history, etc.). Residents’ physical examination results are documented in their personal health account and those at high risk of chronic diseases are screened out. Patients at high risk receive education and follow-up. The details are electronically logged into their account. High-risk residents are referred to general hospitals for re-examination and diagnosis confirmation.

OUTCOMES

• Early-stage cancer screening and management: From June 2008 to 2010, 766,500 residents received physical examinations, and 33,832 high-risk residents were screened with the new IT chronic disease management model.

• The diagnosis rate of early-stage cancer increased by 20% compared with figures for 2007, before the plan was implemented.

• Diabetes and hypertension management: The results are evaluated in two ways: managing rate (% of patients managed by the health system); and effective rate (% of patients whose treatments are effective and conditions are under control).
**KEY CAPABILITIES**

**Political will is the prerequisite:** The Minhang District Health Bureau played a leading role in implementing the health IT system and initiating the chronic disease management plan for its residents.

**Data collection, storage, and analysis capability:** A cloud computing centre was established to collect and store data. This data is transmitted via government web with a capacity of more than 1000M bandwidth. Software is developed to analyse patients’ health information on the hospital and regional levels.

**Diverse stakeholder engagement:** All layers of health organisations (the local health bureau, Centres for Disease Control [China], community care centres, and hospitals) in the Minhang District are involved in use of the e-health system and chronic disease management.

*SINCE 2007, DIABETES AND HYPERTENSION MANAGEMENT AND CONTROL HAS INCREASED, ALONGSIDE TIMELY CANCER DIAGNOSIS*

*Registry rate: % of patients registered/managed by the health system; Effective rate: % of patients whose treatments are effective and conditions are under control.

### Starting Questions for Health System Leaders When Determining How to Set Up Effective Health Informatics Capabilities

The following is a noneexhaustive list of questions to get health system leaders started on developing and/or strengthening any health informatics system that can improve use of medicines.

1. Identify the problem that requires solving (e.g., Is it medication errors? Nonadherence?)

2. Identify the time scale to address the problem (e.g., Do we need the answer now, in a few months, or in a year?)

3. Identify the information required to provide answers to the problem raised (e.g., Do we need patient diagnosis data? Consumption information? Or other data?)

4. Identify the stakeholders that would be needed to validate the required information, problem, and guidance on appropriate information sources (e.g., Should pharmacists be involved? Nurses? Physicians?)

5. Assess the current information collection system to determine the gaps in information from a data and collection process perspective:
   - a. Revision may be needed at different levels from simple to complex (e.g., from adding a data point in collection processes or reformatting existing data for comparability vs. revising an entire collection mechanism within a care setting).
   - b. Assessment should consider time scale intentions: What can be done quickly vs. what may require a longer-term approach.

6. This provides a roadmap for strategies and tactics to fill the gaps:
   - a. Leverage learnings from other countries on how similar data was collected and applied.
   - b. If the level of complexity is relatively high (e.g., not in line with current systems and/or requires new investment and infrastructure), identify the appropriate medium to collect and analyse necessary data (e.g., considerations regarding m-health options vs. EHR vs. paper-based system). Start small: check if a pilot-level intervention works before committing to a national-level investment.
   - c. Do not overestimate the power of digitised information: mistakes and errors may still exist in electronic-based interventions.
   - d. Identify key performance indicators that can be put in place to track progress and value of system.
References


Jiang, X. Personal communication with Xiaohua Jiang (Minhang District Health Bureau, Shanghai, China). Apr., 2012


References continued


Ray, P. and Wimalasiri, J. 2006. The need for technical solutions for maintaining the privacy of EHR. In: *Engineering in medicine and biology society. EMBS 2006: 28th Annual International Conference of the Institute of Electrical and Electronics Engineers (IEEE)*, 31 August-3 September, New York City, US. pp. 4686-4689


Xu, S. Personal communication with Su Xu (Minhang District Health Bureau, Shanghai, China). Apr., 2012
VII. Methodology

Methodology used for the estimate of avoidable costs across 186 countries worldwide
METHODOLOGY USED FOR THE ESTIMATE OF AVOIDABLE COSTS ACROSS 186 COUNTRIES WORLDWIDE

Rationale

Research demonstrates that global information about avoidable costs from suboptimal medicine use is sparse and fragmented. In some countries, particularly high-income countries such as the US, the UK, Canada, and Australia, data is comparatively abundant. Government policy documents make it clear that related adverse events from different levers and related outcomes are being tracked. However, the majority of countries in the world do not have systematic data and information on medicine use. This makes it difficult to identify the starting point for interventions and recommendations.

Scope and sources

In the initial scope of this report, 14 separate levers were assessed to understand the most important levers or contributors to avoidable costs. A pragmatic literature review and expert interviews with health policy advisors from WHO and NICE International were conducted. IMS Institute research identified six primary levers as: nonadherence, untimely medicine use, antibiotic overuse and/or misuse, medication errors, suboptimal generic use, and mismanaged polypharmacy. Each lever was assessed based on the risk of hospitalisation from related adverse events and medicines that may be underused or overused.

The majority of evidence was from English-speaking, high-income countries due to language limitations. There was also a bias towards relative abundance of information in countries with existing, national-level infrastructure for informatics, published articles, and reports. Articles from PubMed, country reports, and private sector reports on specific topics were primary model sources.

Development of initial dataset with existing values

Levers were quantified for countries with existing data. Existing data from literature sources was collated for an initial list of data points for levers. Sources included a combination of peer reviewed and published articles, gray literature, and IMS data. Data estimations were arrived at for each primary lever as follows:

a. Nonadherence

The following approach was applied for the top five chronic NCDs: hypertension, type 2 diabetes, hypercholesterolemia, congestive heart failure, and asthma.

Disease prevalence, likelihood of hospitalisation due to nonadherence, first fill rates of medicines, and hospitalisation costs for each disease were identified using literature sources. IMS Health data on prescriptions and related costs was combined with literature sources by disease for specific countries with available information.

Estimates for the costs of nonadherence were made taking into account medicine and nonmedicine expenditures in a given year using latest available data. Data was adjusted, where appropriate, for the latest year (2009) using consumer price indices from the OECD. This approach likely underestimates the problem given the existing risk of nonadherence during medication intake or once the prescription is filled. However, this approach overestimates by assuming that all people with the disease are taking medicines.

b. Untimely medicine use

Hepatitis B and C avoidable costs were estimated with the following parameters:

- HBV and HCV prevalence.
- Total liver transplants.
- Percent of liver transplants due to HBV and HCV.
- Cost per liver transplant.
- Total avoidable costs.
Avoidable costs due to untimely medicine use in diabetes focused on type 2 diabetes and were estimated with the following parameters:

- Total number of patients with type 2 diabetes.
- Likelihood of developing severe complications from delayed medicine use or unmanaged diabetes. Complications are addressed in the hospital setting and include: myocardial infarction, heart failure, and renal disease.
- Annual cost per patient for complications.
- Total avoidable costs.

c. Antibiotic misuse and overuse

Costs used in this analysis were based on available averages from literature sources. For example, in the US the minimum and maximum cost in 2010 is available from Spellberg et al. 2011 and inflated to 2011 costs using consumer price indices from the OECD (see the Antibiotic section for a full list of references).

d. Medication errors

Costs used for this analysis were limited to hospital-based errors only as this is where the majority of the evidence exists. Data from sources such as the National Priorities Partnership and Institute of Medicine in the US was assessed. This included costs of hospitalisations from errors due to prescribing, transcribing, dispensing, or administering. The medicine cost in this scenario was not included.

e. Suboptimal generic use

Avoidable costs were calculated for countries with existing IMS data based on the percentage of volumes (standard units) that may be replaced with lower-cost generics. It was assumed that 100% conversion to low-cost generics is not possible so a retrospective analysis was conducted to assess potential conversion over a five year period (2006 to 2011). France has made the highest improvement in a select group of countries with available data at 30% conversion over five years. This was the conversion rate used to identify the potential savings in other countries. The price differential between the branded and unbranded generics multiplied by 30% of branded volumes provided the potential avoidable costs.

f. Mismanaged polypharmacy

Data from literature sources was calibrated with IMS data on prescriptions and patient morbidities to inform prevalence of 'major' polypharmacy, described as five or more medicines at once and the likelihood of inappropriate polypharmacy resulting in hospitalisations. Cost of those related hospitalisations were combined to obtain a total cost. Inflation adjustments were made to 2011 using consumer price indices from OECD.

Modelling approach

Once an initial dataset was identified for these six levers, a modelling approach was developed and applied to estimate a global dataset across 186 countries. The methodology assumes that there are factors that drive country differences in what causes suboptimal medicine use. Factor definitions needed to ensure global data availability to assess meaningful differences with real data. The IMS Institute has identified one or more indicators as factor proxies, primarily based on the best available data from sources that provide the most diverse country information, such as the World Health Organization and the World Bank.

Factor and lever relationship: The IMS Institute developed an algorithm to define the impact direction and related weight of the factor on each of the six levers. The direction and weights of each factor was based on research and expert opinion. This approach recognises that not one sole factor influences the final outcome. Instead, it is a blend of dynamics that drives the likelihood of suboptimal use. For example, untimely medicine use is more driven by health system infrastructure and affordability but still affected by other factors. On the other hand, mismanaged polypharmacy is driven more by the proportion of elderly and medicine intensity compared with other factors.
The following steps describe how the model works.

1 Preparation of real-world indicator data

Existing factor values were collected from WHO, the World Bank, and IMS data sources for the latest year (2009) and, where available for 2011, to account for the most representative pool of countries that were the same across all data sources. This filtering process resulted in a basket of 186 countries with 2417 data points across the indicators that contribute to the factor analysis.

This dataset was then normalised on a scale of 1 to 5 for easy comparison. The conversion methodology reflects the nature of the factor so that a score of 5 in Health system infrastructure should mean the country has a relatively high level of health infrastructure. Where the converse is true, i.e., a high value of the factor is associated with a lower likelihood of the associated lever, the reciprocal of the indicator was used before doing the score conversion.
Bands or ranges of values of that indicator were set up for these converted, real-world values that determine the score. The approach used the 3rd percentile and 97th percentile across all the countries for that indicator and split that into five equally spaced bands. The choice of percentile rather than minimum and maximum is to avoid outliers that can compress the scoring system of the other countries; an indicator value that falls outside the range of 3rd percentile to 97th percentile is given a 1 or a 5, as appropriate.

The assumption here is that the relationship between indicator and factor is a linear one. The relationship is unlikely to be that simple, but it is the best assumption made given existing data constraints.

2 Combining proxy indicator values with factor scores

Ten proxy values were used across the five factors. Proxy indicators were combined for health system infrastructure and affordability. For others, proxies were maintained independently as their independent impact on the lever was deemed more interesting to see (e.g., medicine intensity based on volumes in the health system only vs. combined with new chemical entities).

For health system infrastructure and affordability, the mean score was taken across the two and renormalised to be between 1 and 5. This is on the basis that better information on how to combine the indicators does not exist and that each subfactor should be consistently scored between 1 and 5.

3 Converting factor scores to lever scores and calibrating with existing real data

Proxy scores of each country were applied to the weighting table of factor impact (see above) to give a country-specific lever score. It is this lever score that is used to estimate the percentage of avoidable costs out of total health expenditure per country per lever.

Additionally, a single composite factor value for each country was calculated using proxy values. Countries were grouped on the basis of their factors under the assumption that the variation of avoidable costs with the factor score would be consistent for a peer group. The higher the score, the greater the impact on misuse, though the reasons why vary by country.

Each country was then assigned to one of five country groups based on the composite score (using the minimum and maximums). A range was developed based on a split of five equal bands. Each country's composite score was assigned to a band.

4 Initial calibration

Existing values for avoidable costs as percentage of total health expenditure for six levers were identified in specific countries such as the US, the UK, Thailand, South Africa, Australia, Canada, Brazil, China, and India. The model assumes that countries differ from each other in terms of the suboptimal medicine use likelihood and any real data 'base' value. Country likelihoods of avoidable costs were estimated based on their deviation from the composite index factor score.

Real-world factor data and knowledge about how this data contributes to suboptimal medicine use was combined with bands or ranges of values of that indicator to come up with a relative contribution score for each lever by country. The lever score was converted into a nominal likelihood of avoidable cost percentages out of total health expenditure for each lever in each country and then aggregated for the global estimate.

5 Further calibration and error margins

Error margins were introduced to account for uncertainty at two levels: the quality of existing data on the avoidable cost opportunity and the quantity of missing data points. For the quality of existing data, errors between modelled data and actual available data were assumed to be shared by other countries in a similar composite factor score grouping. For example, an error margin for Canada was assumed to be the same error margin for other countries with a similar composite factor index, such as Spain and the UK. Country groupings based on composite indexes like these were used here to create proxy errors for the entire dataset of countries.
To account for quantity of missing data points, error margins were further scaled based on available data in that composite factor index grouping. For example, grouping 1, which includes countries such as Bangladesh, Indonesia, and Ghana have a greater error margin than grouping 5, which includes Canada, the UK, and the US, because greater information exists about the latter and therefore greater certainty can be assumed.

This translates to a ranged value for the level of avoidable costs for each country and an aggregated range across all 186. Table 1 comprises all countries in the model.
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The IMS Institute for Healthcare Informatics leverages collaborative relationships in the public and private sectors to strengthen the vital role of information in advancing healthcare globally. Its mission is to provide key policy setters and decision makers in the global health sector with unique and transformational insights into healthcare dynamics derived from granular analysis of information.

Fulfilling an essential need within healthcare, the Institute delivers objective, relevant insights and research that accelerate understanding and innovation critical to sound decision making and improved patient care.

With access to IMS’s extensive global data assets and analytics, the Institute works in tandem with a broad set of healthcare stakeholders, including government agencies, academic institutions, the life sciences industry and payers, to drive a research agenda dedicated to addressing today’s healthcare challenges.

By collaborating on research of common interest, it builds on a long-standing and extensive tradition of using IMS information and expertise to support the advancement of evidence-based healthcare around the world.
RESEARCH AGENDA

The research agenda for the Institute centers on five areas considered vital to the advancement of healthcare globally:

Demonstrating the effective use of information by healthcare stakeholders globally to improve health outcomes, reduce costs and increase access to available treatments.

Optimizing the performance of medical care through better understanding of disease causes, treatment consequences and measures to improve quality and cost of healthcare delivered to patients.

Understanding the future global role for biopharmaceuticals, the dynamics that shape the market and implications for manufacturers, public and private payers, providers, patients, pharmacists and distributors.

Researching the role of innovation in health system products, processes and delivery systems, and the business and policy systems that drive innovation.

Informing and advancing the healthcare agendas in developing nations through information and analysis.

By collaborating on research of common interest, it builds on a long-standing and extensive tradition of using IMS information and expertise to support the advancement of evidence-based healthcare around the world.

GUIDING PRINCIPLES

The Institute operates from a set of Guiding Principles:

The advancement of healthcare globally is a vital, continuous process.

Timely, high-quality and relevant information is critical to sound healthcare decision making.

Insights gained from information and analysis should be made widely available to healthcare stakeholders.

Effective use of information is often complex, requiring unique knowledge and expertise.

The ongoing innovation and reform in all aspects of healthcare require a dynamic approach to understanding the entire healthcare system.

Personal health information is confidential and patient privacy must be protected.

The private sector has a valuable role to play in collaborating with the public sector related to the use of healthcare data.