Countering Drug Resistance in the Developing World: An Assessment of Incentives across the Value Chain and Recommendations for Policy Interventions

Prashant Yadav

Abstract

The emergence and spread of drug resistance is draining available resources and threatening our ability to treat infectious diseases in developing countries. Countering drug resistance requires pharmaceutical companies, government regulators, doctors, and patients to make difficult choices about drug treatment in order to balance efficacy, cost, safety, and sustainability of drugs. These complex tradeoffs are faced along the drug supply chain from the development of new products, procurement of drugs for donor and government distribution, distribution steps to ensure treatment heterogeneity along with quality and availability, and dispensing and use that requires affordability, patient adherence and rational use of drugs and diagnostics. An analysis of the incentives and risks in the drug supply chain reflects that many stakeholders who can influence optimal prescribing of existing drugs; affect higher patient compliance; and ensure the quality of drugs have weak incentives to carry out these activities optimally. This implies a high potential for drug resistance to accelerate. This paper recommends specific measures to better align the incentives of these stakeholders with resistance-countering activities.

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Working Paper 183
September 2009

Countering Drug Resistance in the Developing World: An Assessment of Incentives across the Value Chain and Recommendations for Policy Interventions

Prashant Yadav
MIT-Zaragoza International Logistics Program

With input from
Emma Back
Rachel Nugent
Jessica Pickett
Center for Global Development

This study was conducted as a part of the Drug Resistance Working Group at the Center for Global Development. The views and opinions expressed in this report are those of the authors and should not be attributed to the Center for Global Development, the MIT-Zaragoza International Logistics Program, the Zaragoza Logistics Center or the policy directors and funders of these research institutes.

This paper was made possible by financial support from the Bill & Melinda Gates Foundation.

Prashant Yadav. 2009. "Countering Drug Resistance in the Developing World: An Assessment of Incentives across the Value Chain and Recommendations for Policy Interventions." CGD Working Paper 183. Washington, D.C.: Center for Global Development.
http://www.cgdev.org/content/publications/detail/1422842

Center for Global Development
1800 Massachusetts Ave., NW
Washington, DC 20036

202.416.4000
(f) 202.416.4050

www.cgdev.org

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FOREWORD

When global supply chains work, they can be miracles of efficiency and innovation, making both those at the top and the bottom better off. But when they fail, the negative consequences can be profound for all who wish to sell, buy, and use the products. Nowhere is this more evident than in the global supply chain for drugs and diagnostic products.

The importance of understanding the supply chain for drugs and diagnostics has been a key part of the work undertaken by an expert working group that CGD convened in late 2007 to examine the global problem of drug resistance. In this working paper, commissioned by CGD to inform the development of the working group's recommendations, Professor Prashant Yadav, MIT/Zaragoza, undertakes a supply chain analysis of drugs and diagnostics. The paper focuses on the ways in which incentives within the supply chain relationships protect (or fail to protect) drug efficacy.

Through structured interviews and independent analysis, Professor Yadav finds that drug and diagnostic supply chain incentive misalignments affect drug markets in developing countries. Among them are differences between generic and branded pharmaceutical manufacturers to protect drug efficacy, moderate incentives for procurement agencies to seek the lowest prices possible, and weak prescriber incentives to adopt diagnostics. Multiple opportunities exist for a better alignment of incentives to protect drug efficacy in the developing world.

In his look across products, and up and down the supply chain, Professor Yadav gives us a whole new perspective not only on what some of the fundamental problems are, but on how specific changes in business practices might make it possible to harness the power of supply chain relationships for greater access to quality medical goods.

Ruth Levine
Senior Fellow and Vice President for
Programs and Operations
Center for Global Development

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EXECUTIVE SUMMARY

The emergence and spread of drug resistance is draining available resources and threatening our ability to treat infectious diseases in developing countries. HIV/AIDS, tuberculosis, malaria, diarrhea and respiratory tract infections continue to be the leading causes of death in many developing countries, many of which have already been exacerbated by resistance. Countering drug resistance often involves complex tradeoffs between activities such as the development of new products; ensuring treatment heterogeneity; and guaranteeing quality and ensuring systemic availability, affordability, compliance, adherence and rational use of drugs and diagnostics. A careful understanding of all the players involved in the resistance problem and their incentives to engage in activities that counter drug resistance is crucial for policy-makers and resource managers in a range of institutions and agencies. This paper presents results gathered through quasi-structured interviews to understand these incentives and develop recommendations to better align them with resistance-countering activities.

Consistent with various earlier studies, this analysis finds that pharmaceutical and large biotech companies have weak incentives to pay adequate attention to the impact of drug resistance or to develop new resistance friendly technologies and narrow spectrum antibiotics, especially those focused towards the developing world. Smaller biotech companies and large generic manufacturers have better incentives to develop and market these technologies. Many large generic manufacturers who are now zealous to enter into the innovation space are more willing to take risks on technologies with smaller market size if they can find opportunities to in-license such products. However, at present, there exists no clear platform to help facilitate such technology transfer. A "science clearing house" which helps unearth all early stage candidates that have some resistance susceptibility benefits and shares this information with interested biotechs, smaller pharmaceutical companies and large generic manufacturers will facilitate the creation of a bigger portfolio of anti-infectives and other technologies.

Many stakeholders who can influence optimal prescribing of existing drugs, affect higher patient compliance and ensure the quality of drugs currently have weak incentives or limited capacity to do so. Most notably, private dispensers and clinics that play an important role in providing diagnosis, the right drug, and appropriate dosing advice for large sections of the population in the developing world do not internalize any of the social costs of drug resistance, and therefore have weak incentives to carry out these activities optimally. Drug regulatory authorities have the mandate and incentives to ensure that drug quality is high across the supply chain and good dispensing practices are followed at all points of drug dispensing. However, their reach and capacity to monitor a fast-growing market of private providers is fairly limited in most developing countries. This paper recommends specific measures to enhance their capacity.

In many countries, drug dispensing franchising and accreditation have emerged (albeit on a small scale) which help maintain consistent quality standards through large networks of geographically dispersed drug outlets. Franchise and accreditation models are scalable ways to ensure that the choice of drugs, the quality of drugs, and the dispensing and dosing practices are optimal, in order to counter drug resistance. This paper recommends the

creation of a global umbrella organization which sets the "meta operating principles" for quality-accredited networks and ensures that quality drugs are dispensed rationally.

Other recommendations include improving the use of diagnostic technologies; collecting data on the volumes of anti-infectives sold; and educating national, social or employer-run insurance and revolving drug fund managers in developing countries on the causes and impacts of drug resistance.

1 Introduction

The emergence and spread of drug resistance is draining available resources and threatening our ability to treat infectious diseases in developing countries. HIV/AIDS, tuberculosis, malaria, diarrhea and respiratory tract infections continue to be the leading causes of death in many developing countries. For many of these diseases, the emergence of resistance against first-line treatments has forced us to switch to more expensive second or third-line agents which prevent resource-constrained countries and health programs from expanding access to life-saving treatments. In some instances, international financing agencies have come to the rescue by providing financing support to developing countries for procuring these expensive medicines. However, this is an unsustainable band-aid, and resistance against second and third-line treatments may also emerge, leaving us without treatment options for some of the most deadly infectious diseases.

The development of resistance is a complex phenomenon with multiple causative factors. Many strategies exist to prevent or contain the emergence of resistance, and, broadly speaking, they can be categorized into two types:

i) Creating incentives that encourage pharmaceutical and biotech companies to develop new drugs to treat infectious diseases and to pay adequate attention to the impact of drug resistance.

ii) Ensuring optimal use of existing drugs through prescriber awareness, higher patient compliance and ensuring drug quality.

Drug resistance has been studied as an economic problem with many facets, such as: information asymmetry about its causes, impacts and costs; negative externalities in costs arising from resistance; and incentive coordination among multiple stake-holders. Previous research (Laxminarayan 2002) acknowledges that drug resistance is a problem of missing incentives among multiple players. Cost and decision economics play an important role in drug resistance; for example, the type of drug (good quality vs. counterfeit, combination vs. mono therapy) a patient obtains at the point of dispensing is dependent upon various cost and health financing factors that pay little heed to drug resistance. Similarly, stock-outs of drugs at the facilities and hospitals and poor functioning of the overall health system also strongly exacerbate the drug resistance problem. Stocking decisions for drugs at the pharmacy and drug store are determined by the cost economics of bearing the expiration and wastage risk from stocking more expensive drugs or stocking cheaper (thus in some cases counterfeit) drugs.

Countering drug resistance often involves complex tradeoffs between activities such as the development of new products, ensuring treatment heterogeneity, guaranteeing product and treatment quality, ensuring systemic availability and affordability of drugs, and adherence and rational use of medicines. The challenge for policymakers is to identify the points of highest leverage and understand the many actors involved, in order to ensure the acceptance and success of any intervention designed to counter the problem of increasing drug resistance. Hence, a careful understanding of the incentives of all players involved in the resistance problem can help policy-makers and resource managers in a range of institutions and agencies formulate effective strategies.

This paper draws from basic decision theory and a set of quasi-structured interviews to understand these incentives and develop recommendations. Through this analysis we seek to answer some (not all) of the open questions, such as:

- How do drug procurement, international financing, health systems strengthening and health policy impact drug resistance?
- What economic determinants influence inappropriate dosing at the prescriber, dispenser and patient level? How do drug price and facility user fees impact drug resistance?
- How does the use of private sector dispensing to enhance access impact drug resistance?
- What incentives issues are preventing appropriate diagnosis before drug dispensing? What is preventing access to improved rapid diagnostics for infections?
- What incentives are needed for pharmaceutical companies to expand research in the discovery of new chemical entities for infectious diseases?
- How can drug resistance considerations be included in the earlier stages of drug development decision models, rather than being a mere afterthought?

Limitations

This paper is an initial exercise intended to clarify thinking about this problem and should be viewed in that context. The focus of the study is on infectious diseases in developing countries. The study has centered more on product distribution than on service provision aspects of the supply chain, so the recommendations and focus of the study will reflect that. Admittedly, the individual behavioral aspects are far more complex, and viewing the product supply chain in isolation may lead to a myopic picture of the issues and solutions. Also, this paper does not explicitly address policies that reduce the spread of infection such as traditional hygiene and infection control measures in hospital settings.

Approach and Methodology

Many decisions across the supply chain, ranging from new drug development to improper usage by the end-patient, impact the emergence of drug resistance, and many distinct organizations and players are involved in making these decisions. We define a "socially optimal outcome" to be the set of decisions at each stage in the supply chain for drugs that minimize the emergence of drug resistance in society as a whole.

There are several possible explanations for why each player may deviate from making socially optimal decisions:

i) Players may not be able to evaluate the socially optimal decisions, because they lack the necessary knowledge or information to make those optimal choices (we term these informational blind-spots).

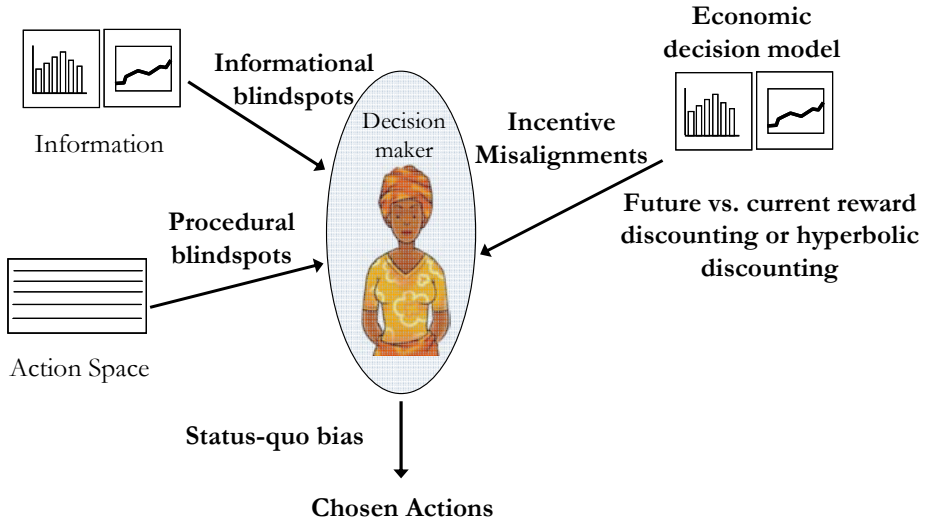
ii) Alternatively, players may knowingly deviate from the social optimum, because they do not internalize all of the costs in their decision making process (incentive misalignments arising to failure to internalize a cost).

iii) Real-life incentive systems tend to reward good immediate outcomes (e.g. lower stock outs of drugs) rather than good long-term decisions (such as maintaining

an assortment of drugs that may lead to decreased resistance). Given that future rewards are heavily discounted as compared to current benefits, delayed emergence of resistance is not rewarded in the incentive structures of most operational players. (incentive misalignments arising from faulty future vs. current reward discounting)

In some instances, the reluctance to deviate from current norms can adversely impact decisions regarding various activities pertinent to drug resistance. Also, interviews have revealed that there exist "procedural blind-spots" where decisions makers believe they are procedurally constrained from making particular decisions, but in reality, it is not the case. Figure 1 below depicts how all of these factors impact decision making.

Figure 1: Decision making and incentive misalignments



Each of the different reasons for deviating from the optimal decision can be mitigated in different ways. i) above can be addressed through better dissemination of information related to the causes of drug resistance and employing a method to counter them (See Back forthcoming for a detailed discussion of this). ii) requires a careful economic analysis of each of the decision points that directly or indirectly affect drug resistance. iii) can be addressed to some extent by creating a stronger reputational risk for the economic actors involved through civil society and public awareness campaigns that address the issue of drug resistance. Creating an environment in which reputational damage from dishonorable dealings would jeopardize long term profits would prevent self-interested short-term profit maximizing actors from squeezing the last dollar of profit out of their current transactions.

This study first identified the key stakeholders and a set of activities that help to counter drug resistance. These were identified based on secondary research, expert interviews and deliberations of the Center for Global Development Drug Resistance Working Group (DRWG). Box 1 below outlines these activities.

Box 1: Activities to Counter Drug Resistance

- Access (availability, affordability & acceptability) to a wider range of (new and innovative) drugs[1]
- Proper diagnosis and optimal prescribing
- Research better dosing regimens for existing drugs[2]
- Lower production cost versions of existing drugs
- Selection, procurement, prescribing and use of only high quality drugs
- Adherence to full dosage, drug regimen and rational use
- Infection prevention in clinical and non-clinical settings
- Development of new vaccines and transmission-blocking technologies

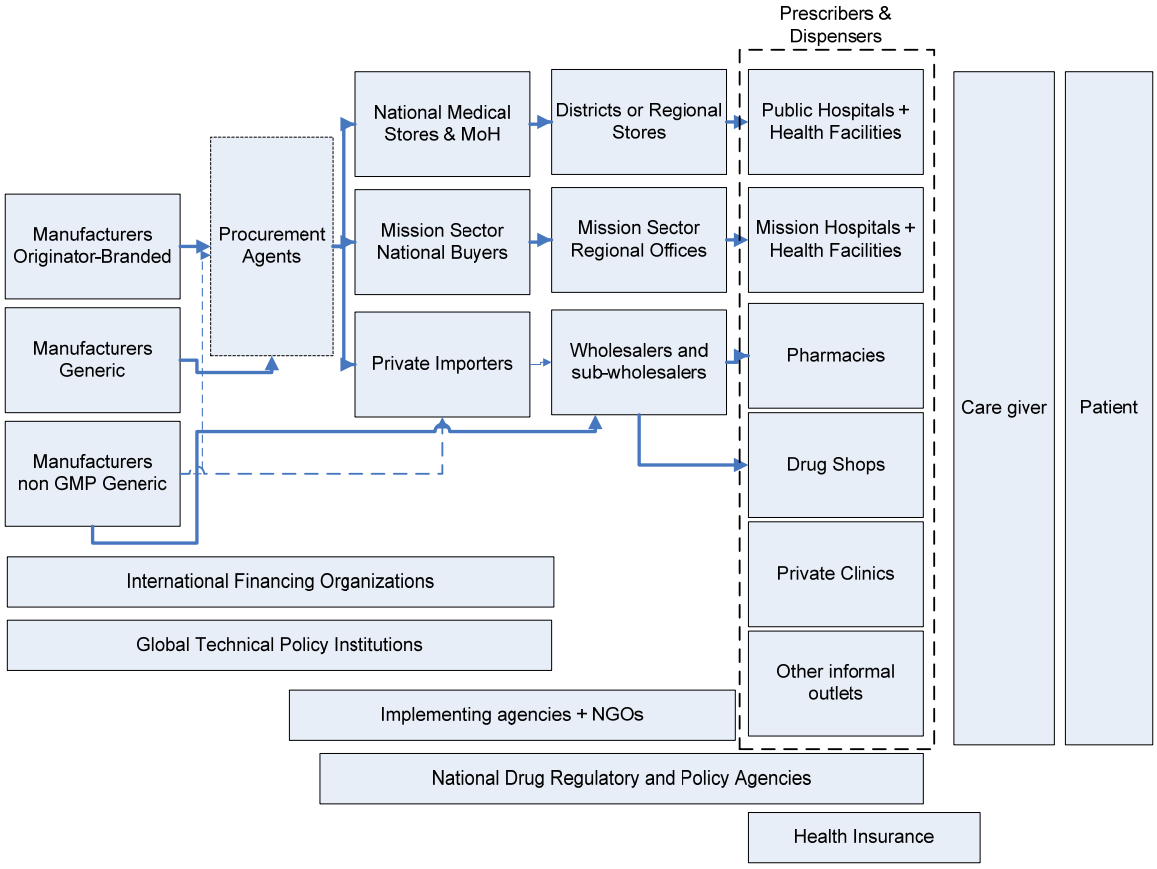
For each of these activities, the decision process of each category of stakeholders was assessed based on interviews with a variety of organizations. Quasi-structured phone and in-person interviews (rather than formal surveys) were used, because the former provide greater flexibility, allowing the respondent to bring up new issues. Fourteen in-depth interviews were conducted between March and September 2008 wherein respondents were asked how they make key decisions related to the activities identified. All interviews were conducted by the investigators themselves. A similar methodology has been used in previous studies of health care value chains (Yadav and Williams 2005; Yadav, Sekhri and Curtis 2007; Lalvani, Yadav, Curtis, Oomman and Bernstein 2008). This approach enabled the partitioning of a complex problem into a number of sub-problems, each representing the decisions and objectives of a distinct player/organization.

Based on an assessment of the decision process, the incentives of stake-holders in each category were classified into: disincentive, weak incentive, medium incentive and strong incentive. This was then used to highlight the key incentive misalignments and suggest policy interventions.

[1] A wider range includes new chemical entities (using similar or different pathways) , combination therapies and enhancements to remaining half life etc. of existing drugs

2 Some research suggests that more intensive and shorter interval doses of anti-infectives may be beneficial for preventing the emergence and spread of resistance. Such research is in many cases limited to antibiotics (Lipsitch and Samore 2002). There is greater need for understanding this for other anti-infectives.

Chart 1: Actors in the value chain for pharmaceutical products in developing countries



A map of stakeholders involved in the value chain for pharmaceuticals was created in order to understand which actors impact decisions pertaining to drug resistance. Manufacturers of pharmaceuticals were sub-categorized into generic, innovative originator and non-GMP generic manufacturers, as their decision processes and incentive structures are very different. Procurement agents are organizations such as UNICEF, IDA, IAPSO, Mission Pharma, and Crown Agents that procure drugs on behalf of national programs and ministries of health. These agents act as a key link between manufacturers and purchasers of pharmaceutical products in many developing countries. The buyers of drugs from manufacturers or procurement agents are divided into public, private and mission to reflect the differences in their decision and incentive structures. The products flow from the buyers to the point of prescribing or dispensing through a distribution channel consisting of regional warehouses and wholesalers. A broad variety of dispensing points such as public hospitals/ clinics, mission hospitals, private clinics, pharmacies, drug shops and informal outlets were studied and included in the analysis. National and supranational drug regulatory authorities such as the WHO Prequalification program have a key role in ensuring high drug quality and proper

drug selection for a country. Global technical agencies are institutions such as the WHO which provide technical guidance and set reference standards on treatment guidelines and help define essential drug lists for countries. Financing organizations such as the World Bank, the Global Fund and bi-lateral donors provide financing for drug procurement and health system improvement and, thus, are also key players who may impact drug resistance.

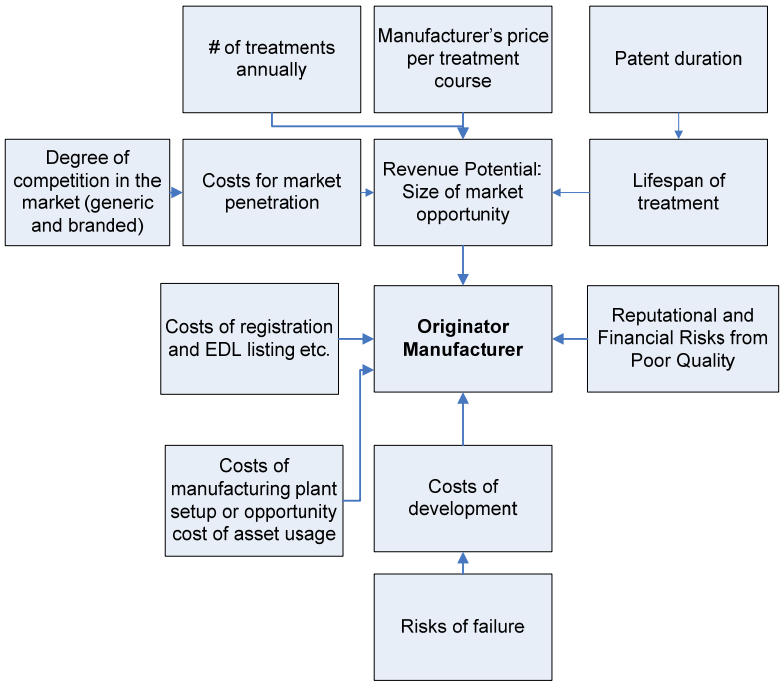
2 Decision Influencers and Incentives

For each stakeholder identified in the previous section, decision models were elicited using the interview methodology described earlier. These decision models, along with incentive assessments for key activities that influence drug resistance for each player, are presented below.

Originator manufacturers

Manufacturers of innovative drugs, vaccines (and to some extent diagnostic technologies) use a decision model driven primarily by the size of the market opportunity and the risks of failure of a technology. In addition, manufacturers responded that the degree that market competition increases their costs of market penetration, especially in markets where the drug candidate is only an improvement on an available dosing regimen. On the other hand, higher risks of failure weighed against a small market size and prevent companies from developing new classes of products that are significantly different from existing products in their mechanisms of treatment.

Chart 2: Originator Manufacturer's Decision Model



The low price per treatment that a manufacturer can charge due to affordability and corporate responsibility pressures for products targeted for the developing world makes this decision process not work in favor of new, innovative drugs or vaccines for infectious diseases, unless they have a reasonable market in high income countries. For antibiotics in

particular, the low reimbursement for antibiotic treatment in high-income countries also undermines incentives to produce new, innovative products. Although longer patent durations may help marginally tilt the decision model in favor of development of new classes of drugs and vaccines for infectious diseases, this would not necessarily alleviate the broader problem. Originator manufacturers also internalize the risks from poor quality products being dispensed downstream in the supply chain. In environments where this risk is high, this impacts their choice of channels for distribution and may lead to a lack of competition in the distribution channels and, in some cases, a product being handed-over to a third party importer/ agent at an early stage in the supply chain. In some instances, Corporate Social Responsibility (CSR) acts as a driver to balance profit-based decision models which have led to a few isolated large investments in the development of drugs targeted for infectious diseases of the developing world (e.g. Coartem from Novartis). However, pharmaceutical companies do not see big CSR benefits from out-licensing early stage compounds which may have benefits from a resistance standpoint. On the other hand, out-licensing (even if at early stage) does have its associated legal and contractual costs; and hence, the incentives for a pharmaceutical company to seek such opportunities are very weak. For somewhat similar reasons, they have poor incentives to work with partners on developing co-formulated products. Pharmaceutical companies may limit the list of indications/symptoms for which an anti-infective product can be dispensed and can also educate the channel about these indications. This can have a real impact on countering resistance, but they do not have the incentives for expending effort and resources on this activity.

Table 1: Incentives of Originator Manufacturers

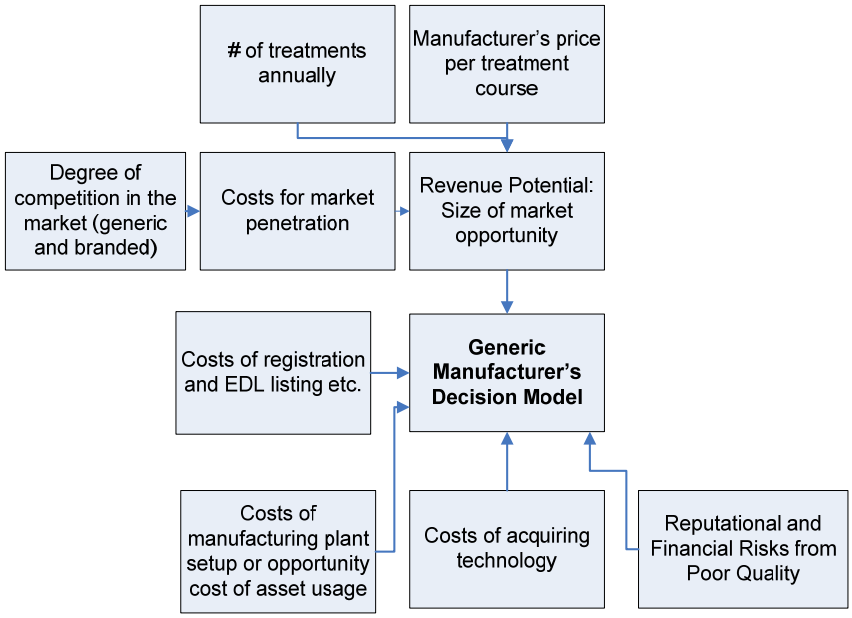
Development of new drugs*/vaccines	**WEAK**
Development of enhanced versions of existing drugs	**WEAK**
Development of co-formulated products with partners	**WEAK**
Out-licensing early stage compounds with resistance benefits	**WEAK**
Ensuring consistent high quality across the supply chain	**MEDIUM**
Influencing optimal prescribing and proper diagnosis	**MEDIUM**
Educating for rational use	**MEDIUM**
Reducing prices of new or existing drugs	**WEAK**
Reserving a product for future use	**WEAK**

* Note that we specifically refer to the incentives for drugs/vaccines targeted towards infectious diseases with a higher prevalence in the developing world

Generic Manufacturers

Manufacturers of generic products have a slightly different decision model. They evaluate a potential generic drug based on size of market, cost of penetration and the cost of acquiring the technology. The costs related to marketing approval/registration of a generic product (chemical or bio-equivalence studies, dossier submission etc.) in each country are considered a significant cost by many generic manufacturers. While there are many innovative manufacturers that also have generic products in their portfolio, in such cases we refer only to their generic business.

Chart 3: Generic Manufacturer's Decision Model



Many large generic manufacturers are keen to get into pharmaceutical classes that have been traditionally dominated by big pharmaceutical companies. They have little experience registering and obtaining marketing approvals and are willing to get on the learning curve by in-licensing late or mid-stage compounds which originator companies do not find attractive. They are willing to do this even for products with small revenue potential solely for the benefit of gaining this experience and then leveraging the knowledge to demonstrate credibility as an innovative drug manufacturer. In many cases, generic manufacturers have strong sales forces in low income countries and want to expand the portfolio of products that their sales rep promotes on each physician or dispenser visit.[3] The case of Aspen Pharma in South Africa is worth studying in detail for this purpose.

South Africa-based Aspen Pharmaceuticals is Africa's largest pharmaceutical manufacturer and has businesses in South Africa, Australasia, India, East Africa and also exports across the globe. Aspen is also a leading global player in generic anti-retrovirals. In June 2008, Aspen acquired four core branded GlaxoSmithkline (GSK) products – Eltroxin, Imuran, Lanoxin and Zyloric – which provided Aspen an opportunity to learn more about the process of IP in-licensing. For GSK it provided an opportunity to recover some value from off-patent IP. Similar models can be used for out-licensing of products with small market potential for large pharmaceutical companies but are still good candidates for generic manufacturers.

[3] Sales forces of generic manufacturers (and also innovative manufacturers) in low income environments target pharmacies and wholesaler establishment over the conventional developed country model of targeting prescribing physicians.

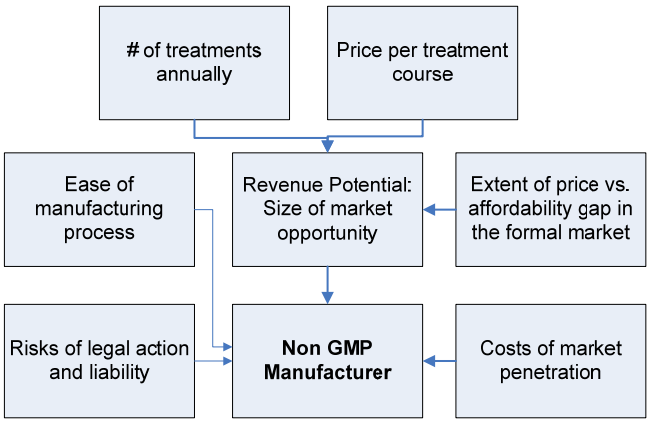
Table 2: Incentives of Generic Manufacturers

Development of new drugs/vaccines	**N/A**
Development of enhanced versions of existing drugs	**MEDIUM**
Development of co-formulated products with partners	**N/A**
In-licensing mid to late-stage compounds with resistance benefits	**STRONG**
Ensuring consistent high quality across the supply chain	**MEDIUM**
Influencing optimal prescribing and proper diagnosis	**WEAK**
Educating for rational use	**MEDIUM**
Reducing prices of new or existing drugs	**STRONG**
Reserving a product for future use	**N/A**

Non-GMP generic manufacturers

Generic manufacturers in developing countries which are not fully GMP compliant have a very different decision model as compared to innovative and GMP generic manufacturers.

Chart 4: Non-GMP Generic Manufacturer's Decision Model



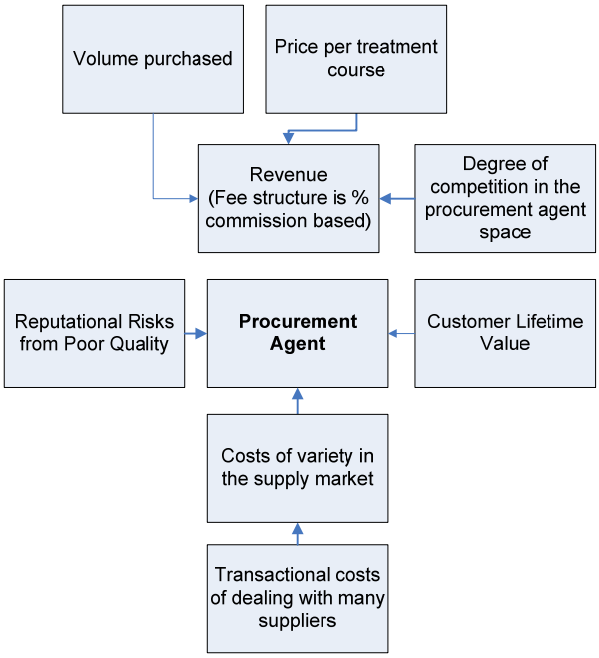
For the non-GMP manufacturer, the driving factors are the extent of the affordability gap in the prices for drugs produced by GMP manufacturers, the ease of the manufacturing process and the risks of potential legal liability in the country of sales. All three of these can be successfully used to drive non-GMP manufacturers out of the market or help them graduate to becoming GMP manufacturers.

Procurement agents

Procurement agents act as vital link between manufacturers and the aggregated buyers (national governments, importers) of drugs in developing countries. As such they can play a

key role in advising countries on drug and supplier choice, impact of drug variety and heterogeneity, etc.; however, their current role remains purely of transaction processing and does not include full service provision.

Chart 5: Procurement Agent's Decision Model



In addition, maintaining a larger variety of drugs in their catalog requires them to establish relationships with multiple manufacturers and suppliers which requires greater transactional cost. While their incentive structures are not necessarily geared to favor maintaining relationships with multiple suppliers, customer service considerations lead them to do so.

Table 3: Incentives of Procurement Agents

Negotiate lower prices with manufacturers	**MEDIUM**
Select quality suppliers and conduct pre-shipment inspection	**STRONG**
Maintain relationships with multiple suppliers for each product	**MEDIUM**
Disseminate information and technical assistance to countries on resistance related issues and optimal drug selection[4]	**WEAK**

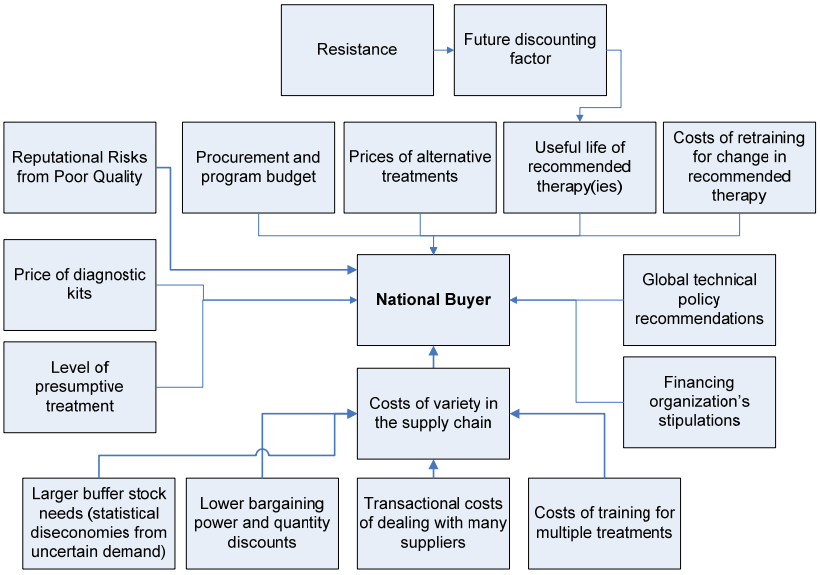
National Buyers

Pharmaceuticals are second only to salaries as the most significant proportion of government and private out-of-pocket expenditures in most low and middle-income countries. Total pharmaceutical expenditures are up to 40% of the health care budget in many countries in sub-Saharan Africa. Thus, ministries of health have a very involved decision process to select

[4] In tune with guidelines set by global technical agencies such as WHO

drugs to be included in the national health programs. Price comparisons, budget availability and recommendations from global technical agencies drive the drug selection process. The useful life of a recommended therapy is also used in the selection process. However, there are clear costs resulting from drug heterogeneity whereas the benefits of heterogeneity are not clear or have a future discounting problem. The cost of heterogeneity include higher prices from suppliers, need for higher buffer stock and the cost of training health workers on the recommended prescribing algorithm if there is drug heterogeneity.

Chart 6: National Buyer's Decision Model



The value from increased treatment heterogeneity is a global benefit that is not fully internalized by the national buyers. The presence of significant costs due to treatment heterogeneity further weakens their incentives.

Similarly, the cost-benefit analysis of diagnostics, in some cases, (for example malaria) does not always favor their large scale use. For instance, if the cost of diagnostics is high, a planner with limited budget who does not internalize the long term cost of resistance would not realize the benefits from their use.

Some countries have shown reluctance to adopt new innovative drugs or vaccines quickly into their national programs due to the high costs of retraining and the reputational risks from use of drug and vaccine technologies that have yet to be rolled out by other countries in the region.

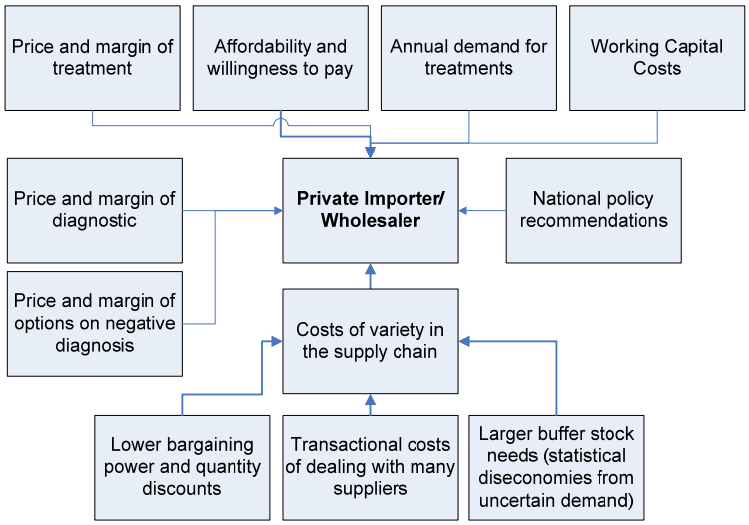
Table 4: Incentives of National Buyers

Select new innovative drugs for inclusion in national essential drugs list	**MEDIUM**
Select high quality products and combination therapies	**STRONG**
Recommend multiple first line therapies	**WEAK**
Procure and promote the use of diagnostic kits	**WEAK**
Influence optimal prescribing through provider education	**STRONG**

Private Importers, Wholesalers and Pharmacists

Similarly, private importers, wholesalers and pharmacists also face the costs resulting from stocking a wider assortment of drugs for higher treatment heterogeneity. Their stocking decisions are based on the annual demand, price and margin of the treatment option and the willingness to pay (WTP) of the end-patients.

Chart 7: Private Importer's/Wholesaler's/Pharmacist's Decision Model



The private wholesalers and distributors have a weak incentive to stock and promote the use of diagnostics or to maintain stocks to enable treatment heterogeneity. This results from the margins being low and the willingness-to-pay for diagnostics being lower than that for drugs (Naing et. al, 2000)

Table 5: Incentives of Private Importers/Wholesalers/Pharmacists

Select and stock quality products	**MEDIUM**
Stock and promote the use of diagnostics	**WEAK**
Stock a larger variety of treatment options	**WEAK**
Ensure affordability of new products	**MEDIUM**
Influence optimal prescribing through provider education	**WEAK**

Global Technical Agencies

Technical agencies such as the WHO help countries select their essential drugs list and influence policy recommendations, which may impact drug resistance in multiple ways. The inclusion of a drug in their recommended treatment options are driven primarily by factors such as scientific committee assessments, robustness of safety and efficacy data, resistance surveillance and affordability in the market. In some cases such as rapid diagnostic tests, the

global technical agencies also have to consider the risks from false negatives in recommending treatment guidelines. There is also a non-negligible cost associated with creating a communication campaign and redesigning training material every time a treatment guideline is changed. Thus, global technical agencies do not always have the incentive to recommend treatments and guidelines which may work towards countering drug resistance. The global technical agencies are conservative in their approach, and rightfully so, given the reputational and patient risks from issuing incorrect guidelines. Similarly, global technical agencies do not currently have the incentives to recommend a large variety of first line treatments for each disease.

Chart 8: Global Technical Agencies' Decision Model

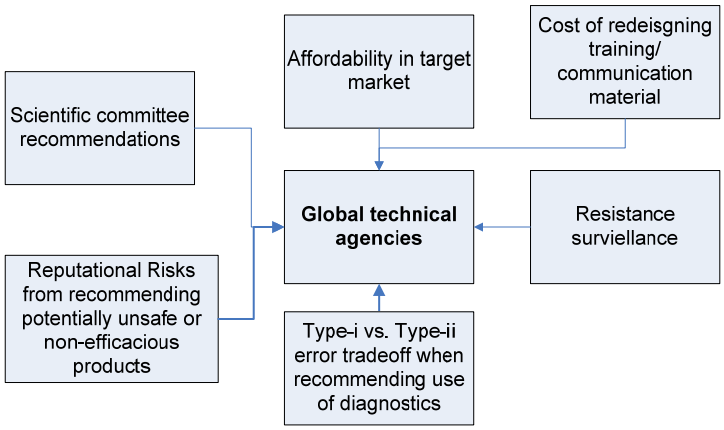
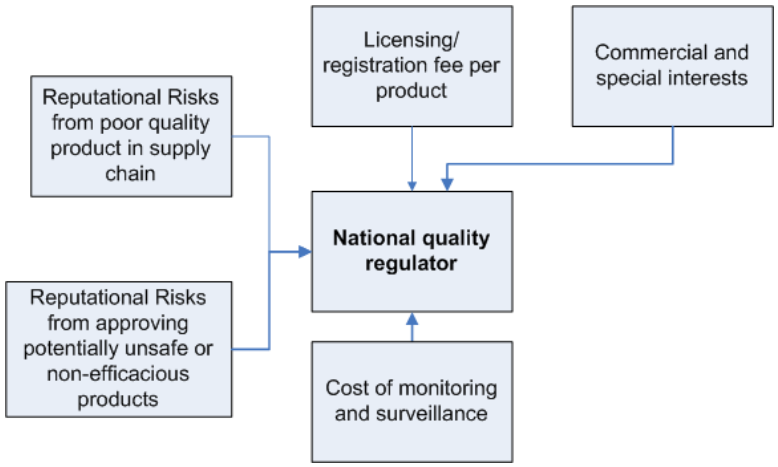


Table 6: Incentives of Global Technical Agencies

Recommend inclusion of new products on essential drugs lists	**MEDIUM**
Promote the use of diagnostics through policy recommendations	**MEDIUM**
Encourage prevention , infection control and immunization coverage	**STRONG**
Recommend a larger variety of first-line treatments to countries	**WEAK**
Influence optimal usage through provider and patient education	**STRONG**

National Quality Regulators

Chart 9: National Quality Regulator's Decision Model



Effective regulation of drugs is a key component in ensuring quality of drugs and their rational use. The unregulated supply of drugs or poor quality of drugs can accelerate the development of drug-resistant strains of infectious diseases. Drug regulatory authorities engage in licensing and product registration; inspection of manufacturing, warehousing and dispensing facilities; post marketing surveillance; and control of drug promotion and advertising.

Typically, drug regulatory authorities receive some degree of support from the government budget, and the remaining part is financed through registration fees. The level of the registration fees must be commensurate with the size of the market, and make it sufficiently profitable for the manufacturer or its agent to register the product. Prohibitively high registration fees lead to fewer products registered in the country and decrease treatment heterogeneity.

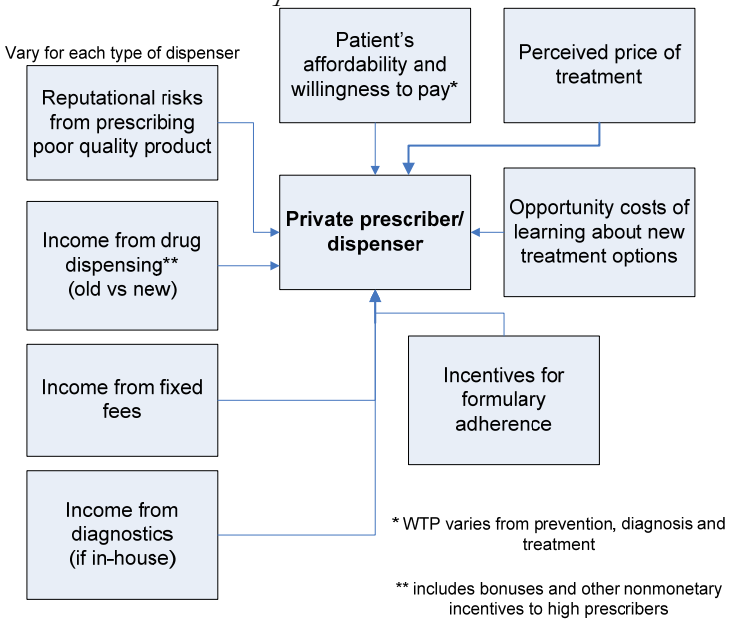
Table 7: Incentives of National Quality Regulators

Ensure the availability of a wide variety of treatment options	**STRONG**
Ensure quality products throughout the supply chain	**STRONG**
De-register old and obsolete products	**MEDIUM**
Expedite approval of new products	**MEDIUM**
Require manufacturers to collect and report data on distribution, import and export of anti-infectives	**WEAK**

Drug regulatory authorities have poor incentives to ensure that manufacturers report data on types of anti-infectives produced, imported and sold in their country. This data can be crucial to understanding drug resistance but currently does not exist in a systemic manner. This is not a mandate clearly laid for drug regulatory authorities. Apart from that, drug regulatory authorities do not face an incentives issue, but rather a severe capacity constraint, in their ability to monitor the quality of drugs dispensed. In some cases, commercial and trade lobbies influence the decisions of the drug regulatory authority, and it is, thus, important to create transparent financial systems for drug regulatory authorities.

Prescribers and Dispensers

Chart 10: Prescriber's and Dispenser's Decision Model



Private dispensing clinics, which are an important source of medicines outside the public sector for certain diseases such as diarrhea and respiratory tract infections, often have a multi-stream revenue model from fixed consultation fees, margins from drug dispensing, and income from diagnosis. Their prescribing and pricing choices are, thus, driven by the patient's willingness to pay for each of these. The WTP varies significantly, with higher WTP for treatment than for fixed fees or diagnostics. This creates a system of perverse incentives at the dispensing clinic and prevents optimal prescribing. Also, prescribers select treatment based on patient's perceived affordability and a perceived availability in the market. The prescriber's perceived price of treatment is not always the true market price and also the availability may be different from the perceived availability (information asymmetry on price for the prescriber).

It is also interesting to understand the prescriber's incentives related to treatment based on confirmed diagnosis. When a patient presents with symptoms that could be caused by different type of infections (e.g. malaria or pneumonia) the health care providers can either prescribe a therapy based on her based judgment or wait until a diagnostic test confirms the nature of disease. The decision to prescribe or dispense a treatment immediately gives the patient something tangible to take away from the visit and thus makes her have a better perception of the health care provider. Similar incentives govern the prescription of broad spectrum antibiotics over narrow spectrum antibiotics. Thus in the absence of quick and cheap diagnostic methods, prescribers in many low income environments do not have an incentive to await detailed diagnosis before prescribing. This factor differentiates low income markets from middle and high income markets where prescribers may realize income/revenue share from diagnosis or in some cases have a high risk of liability if they prescribe without confirmed diagnosis.

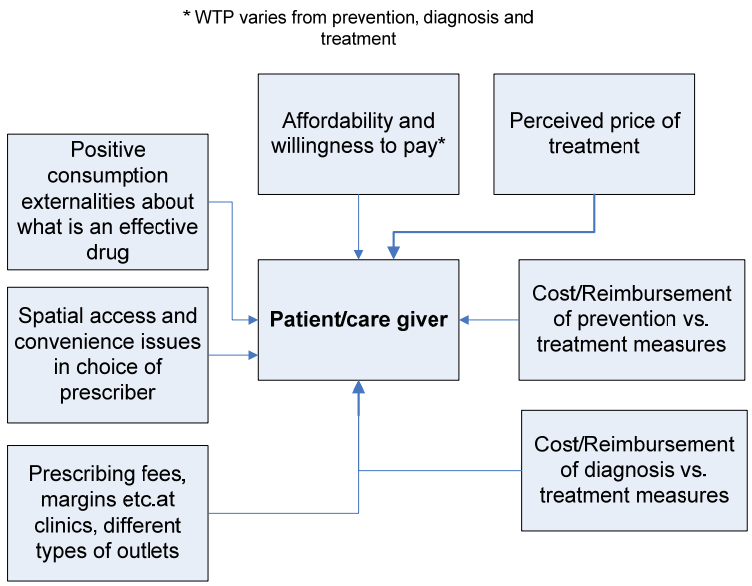
In many developing countries, the prescribers have little ability to update their knowledge about new treatment options as there is no concept of Continuing Medical Education (CME) nor are there sales representatives who educate the prescribers about new treatment options. The prescribers face a huge opportunity cost of learning about new treatment options and changes in indications for specific products. Also, given the prescriber's reward structure, they have no incentives to expend effort in educating patients about infection control measures.

Table 8: Incentives of Prescribers and Dispensers

Appropriate use of diagnostics	**VARIES**
Educate patient/care giver about dosage, adherence etc.	**MEDIUM**
Educate patients on the importance of measures to prevent infection, such as immunization, vector control, use of bednets, etc.	**WEAK**
Prescribe in accordance with formulary/ third party payer's reimbursement structure	**STRONG**

Patients and Care-givers

Chart 11: Patient's and Care-Giver's Decision Models



The patient or care-giver's choice model of where to seek treatment largely influences the type and quality of treatment and advice he/she will receive. Thus, it becomes critical to understand the relative importance of spatial access and convenience factors vs. prescribing fees and other cost factors in the patient's treatment-seeking choices. Also, in cases where there is a social or private insurance system in place, the varied reimbursement rates for prescriber fees, diagnosis costs, and treatment costs can influence the patient and prescriber choice of diagnosis vs. presumptive treatment. Patients have weak incentives to engage in infection control activities primarily because of "informational blindspots" (the prescriber

does not educate them well on these). Information about the benefits and operational modalities of infection control is limited, with public health messages often being the only source.
In addition to the rational economic incentives that were elicited here, in many cases, cultural norms and other factors influence the patient's decision model. Acknowledging that it is not easy to understand these and they vary from region to region, the above schematic illustrates several of the factors that patients and care givers account for in their decision model for obtaining treatment.
Table 9: Incentives of Patients and Care-Givers

Select the right prescriber/dispenser (self-medication vs. clinic etc.)	**MEDIUM**
Optimal dosage and adherence	**WEAK**
Make or influence the right choice of drug	**STRONG**
Engage in prevention, infection control, vector control etc.	**WEAK**

3 Recommendations for Policy Intervention

Acknowledging that complex institutions such as the pharmaceutical supply chain in developing countries change slowly and celebrate incremental advances, a set of recommendations are presented in this section that attempt to remedy the incentives misalignments highlighted in the previous sections. The recommendations chosen are based on two criteria: practicality and the ability to rectify more than one incentive misalignment. Many of these recommendations would require further analysis to be translated into implementable actions.

Create a science clearing house for resistance related technologies
There exist clear opportunities to counter the progression of drug resistance through resistance-slowing drugs and other technologies. However, profit-driven originator pharmaceutical companies may not have the incentives for developing such new drugs, vaccines, and diagnostics. Smaller biotech companies and large generic manufacturers may have better incentives to develop and market these technologies, as many large generic manufacturers eager to enter into the innovation space are more willing to take risks on technologies with smaller market size if they can find opportunities to in-license such products. However, at present there exists no clear platform which can help facilitate such technology transfer.

Product Development Partnerships (PDPs) such as MMV (Medicines for Malaria Venture) and DNDi (Drugs for Neglected Diseases Initiative) have successfully demonstrated how mid to late-stage research from academic and pharmaceutical research laboratories can be leveraged to generate a healthy portfolio of new drugs. A "science clearing house," which helps unearth all early stage candidates with resistance susceptibility benefits and shares this information with interested biotech, smaller pharmaceutical companies, large generic manufacturers, and donors looking to move them forward will facilitate a bigger portfolio of anti-infectives and other technologies. In addition to technology identification and matching,

the clearing house ideally could also play some role in contractual and legal issues pertaining to out-licensing, thereby reducing the associated transaction costs. This would reduce the disincentives for pharmaceutical companies who come across candidates with interesting properties from a drug resistance standpoint but can neither follow them through the development process nor out-license them due to the lack of a clear, expedited and cost-efficient mechanism to do so.

The clearing house could be organized as an online workspace which connects all researchers and funders – in pharmaceutical or biotech companies, academia, government, generic manufacturers, NGOs and donors – working on or interested in potential technology candidates with resistance-slowing or reversing potential. The clearing house would allow partners to evaluate and share information and create a forum that promotes communication, collaboration and efficient information dissemination about resistance related technologies in discovery and pre-clinical stages. International donors and funders of global health research would be the likely candidates to establish such a clearing house, with much of the early content populated by academic, public sector and non-profit researchers.

There are a growing number of examples of web-based marketplaces. With broad buy-in from companies, academics and non-profits, U.S.-based Collaborative Drug Discovery (CDD) uses a for-profit, subscription model to attract collaborators . It has recently received funding from the Gates Foundation to make its platform freely available for TB researchers. Open Source Drug Discovery (OSDD) employs a completely open source platform for researchers and developers of drugs solely for neglected diseases. With initial funding from the Indian government, OSDD creates collaborations between academic and government researchers that have accelerated scientific activity, such as gene sequencing. The incentives to use new tools for research collaboration are clear: laboratory researchers and product developers seek greater opportunities to move their ideas beyond the laboratory; companies and funders may find the opportunity to lower transactions costs of searching for in-licensing and financing drug and other technology candidates.

Strengthen capacity of national drug regulatory authorities to carry out inspection and post-marketing surveillance

Drug regulatory authorities in most developing (and also developed) countries are focused more on licensing, product registration and marketing approval rather than on facility inspection, post-marketing surveillance and monitoring. Thus, there is little check on unlicensed manufacturers, importers, wholesalers and retailers who sell counterfeits and/or products of unknown quality. External budgetary support to drug regulatory authorities can provide them with an increased ability to ensure that only high quality drugs are available and proper dispensing practices are followed. In the absence of such support, the regulatory authorities of most developing countries remain resource-constrained and unable to carry out facility inspection or quality control tests at points of manufacture, storage or dispensing.

Create a global umbrella organization for quality-accredited drug franchise shops in developing countries

Private dispensers and clinics play an important role in providing diagnoses, the correct drug treatment and appropriate dosing advice; however, their incentives are not aligned to carry out these activities optimally, and they do not internalize any of the social costs of drug

resistance. Drug regulatory authorities have the mandate and incentives to ensure that drug quality is high across the supply chain and good dispensing practices are followed at all points of drug dispensing; however, their reach and capacity to monitor a fast-growing market of private providers is fairly limited in most developing countries. Drug dispensing franchise networks have emerged in many countries that help maintain consistent quality standards through large networks of geographically dispersed drug outlets. Such franchise networks scale well, and, in addition to guaranteeing good drug quality and dispensing advice, they achieve economies of scale in distribution, information systems, and operational management. This model has been used with reasonable success in Ghana (GSMF Care Shops), Kenya (CFW Shops) and Tanzania (ADDO shops) to achieve the dual objective of improving access to drugs, while maintaining the high quality of drugs and dispensing.

In addition to ensuring the high quality of drugs and other products available, these franchised drug outlets can also engage in other efforts to decrease information asymmetries and provide incentives for rational use behavior. For example, these drug outlets can use resistance-specific checklists for employee adherence during each consumer interaction. And they can engage in drug resistance information campaigns on both sides of the counter: requiring dispensers to attend continuing professional development courses and engaging in consumer education and outreach to pass that information along both formally (public sessions) and informally (day-to-day interactions).

While the franchise model has proven to be a scalable way to ensure the optimal choice of drugs, quality of drugs, and dispensing and dosing practices to counter drug resistance, to this day, these initiatives have been small in scale and restricted to limited geographies. The creation of a global umbrella organization which sets the "meta operating principles" for the franchises and ensures the rational dispensation of high quality drugs could foster the proliferation of these quality-accredited drug dispensing outlets and clinics. This organization needs to create a global brand of quality for drug dispensing and work to improve the role of the drug regulatory authorities as the guardians of quality in the distribution chain.

Mandate drug regulatory authorities to collect and report data on distribution, import and export of anti-infectives

Currently, there is very little information available on the quantity and type of anti-infectives dispensed in the developing world. Metrics that look at population demographics, disease incidence and anti-infective consumption are essential to understanding and proactively managing the development of drug resistance. Such metrics can only be developed when there is accurate data on the volume of anti-infectives sold in each country. If these data are collected with sufficient demographic granularity, researchers can use it with resistance surveillance data to better understand the factors that contribute most to the development of resistance. Admittedly, this is an ambitious objective, but regions such as ECOWAS, where some degree of coordination exists across national drug regulatory authorities, would be a good place to jump-start such an initiative. In addition to being able to better understand the development of drug resistance, such data will also provide numerous extra benefits, such as: better understanding of the markets in general, better track and trace ability for anti-infectives, and a more stringent control on anti-infectives of spurious quality.

Create incentive structures to promote enhanced use of diagnostics

Unnecessary drug use could be prevented and a shift to more targeted resistance-friendly treatments would be facilitated if rapid diagnostic tests were available and affordable, and if there were clear financial incentives for health care providers and patients for their use. In the last decade technological investments have led to the availability of several new rapid diagnostic tests .Despite the availability of point of care diagnostics, due to the lack of incentives for national health programs, distribution channel players and the prescribers/dispenser to adopt these technologies, their uptake has been fairly limited. The willingness to pay for diagnostics is lower than that for treatments, which results in weak incentives for the actors involved in distribution and dispensing to promote the use of diagnostic technologies. Although the cost of some diagnostic technologies – like the RDT for malaria – has fallen, they still remain beyond the WTP threshold of end-patients and prescribers. This gap can be managed through higher international financing and a focus on diagnostics that can be used in primary care settings. Access to diagnostics remains an under researched area, and new models of delivery such as bundled pricing for diagnostic technologies should be studied.

Better educate national, social or employer-run insurance and revolving drug fund managers in developing countries on the causes, impacts and strategies to contain drug resistance

In countries where there exists a social insurance scheme (e.g. Ghana, Kyrgyzstan), a reasonable penetration of employer-provided insurance or health care (Zambia with copper mines, Ghana with gold mines and cocoa plantations), or a large revolving drug fund (Sudan), these systems can be used as points of high leverage to ensure that dispensers and prescribers offer "resistance-friendly" products and place adequate emphasis on infection control. This could be achieved by creating a forum where all insurance or revolving drug fund managers in developing countries can come together to share their experiences. The forum could be used to emphasize messages about how payers can leverage their buying power to influence rational use, dispensing and use of diagnostics.

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