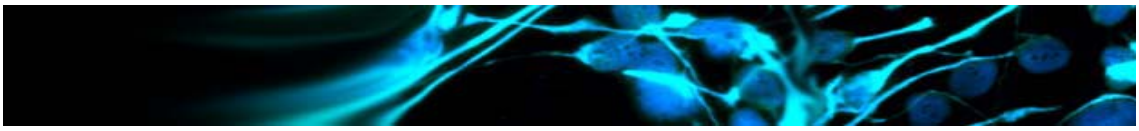
OHE Research
Office of Health Economics

Occasional Paper 11/04

Drugs and Vaccines for Developing Countries

Adrian Towse
Eric Keuffel
Hannah E. Kettler
David B. Ridley

21 May 2011



Drugs and Vaccines for Developing Countries

Office of Health Economics
Occasional Paper 11/04
21 May 2011

Adrian Towse, OHE
Eric Keuffel, Temple University
Hannah E. Kettler, Bill and Melinda Gates Foundation
David B. Ridley, Duke University

Corresponding author: Adrian Towse, Southside, 7th Floor, 105 Victoria Street, London SW1E 6QT

Tel: +44 (0)20 7747 8855, E-mail: atowse@ohe.org

About the authors

Adrian Towse is Director of the Office of Health Economics and Visiting Professor at the Department of Economics and Related Studies at the University of York.

Eric Keuffel, PhD, is Assistant Professor, Risk, Insurance, and Healthcare Management, at Fox School of Business, Temple University.

Hannah E. Kettler, PhD, is Senior Program Officer for Industry Relations, Global Health Office of the President, Bill and Melinda Gates Foundation.

David B. Ridley, PhD, is Assistant Professor at The Fuqua School of Business, Duke University.

Acknowledgements

A version of this Occasional paper will be published as a chapter in the *Oxford Handbook on the Economics of the Biopharmaceutical Industry*, edited by Danzon and Nicholson, to be published in 2012.

This Occasional Paper is the work of the authors and does not necessarily represent the views of the Office of Health Economics, Temple University, the Bill and Melinda Gates Foundation or Duke University.

Contents

1. Introduction

The pharmaceutical industry faces many challenges in addressing the health needs of the poorest in middle and low income countries (MLICs). The economic issues related to pharmaceuticals for these patients differ depending on whether the medicine treats a "global disease" (a therapeutic category which has a substantial existing market in high-income countries) or a "neglected disease" (one that largely afflicts only those in low-income countries)[1]. In the case of the former, medicines widely available in richer countries often are unavailable or unaffordable in poorer countries for a variety of reasons including: an inability to afford to buy out-of-pocket; limited health insurance; poor delivery infrastructure; fiscally restricted governments; and weak regulatory and governance capacity. In the case of neglected diseases, subsidies and policies to mitigate risk are required to motivate for-profit companies to develop effective medicines and even then the resulting products may not be affordable.

Much has changed over the past decade. Multinational companies (MNCs) in partnership with academia, not-for-profits, governments and foundations have increased funding and effort to develop new technologies for HIV/AIDS, TB, malaria, and some other tropical diseases (Moran et al., 2011). Local drug and vaccine companies in emerging markets, such as India, China and Brazil, are also investing resources in innovative solutions for neglected diseases as they try to evolve from low cost generic product suppliers into R&D based companies (Frew, Liu and Singer, 2008). Government and philanthropic funding to assist low-income countries with procurement of some "global" medicines and vaccines has increased these products' availability for poor populations. In addition, the growth in GDP per capita, expansion of the middle class and, in some emerging market countries, the extension of health insurance has motivated profit-seeking manufacturers to view some MLICs as an important source of future revenue growth. Many are exploring innovative marketing and pricing strategies in an attempt to expand sales and increase availability, including differential pricing where the lowest income groups secured the lowest price for drugs and vaccines.

The strategic philosophy of some of the MNC leaders is also starting to change. There is increased recognition that they need to make a substantive contribution to global health. And to make those contributions sustainable, they require approaches that are both commercially viable and socially credible. Some groups like the Access to Medicines Foundation, based in the Netherlands, are actively monitoring what companies are doing, ranking performance against best practice (Mehrpouya et al. 2010). Arguably this instrument, which uses a transparent

[1] WHO organizes diseases into three categories – global, neglected and very neglected. We discuss all three in Section 2 but have grouped Type II and III together for the purpose of this summary.

challengeable mechanism, serves both companies and their critics as they work to solve the health problems of the poorest.

In this paper we set out the context for the problem of insufficient affordable medicines to address health issues in developing countries. We also highlight some of the drivers of recent positive trends. We then detail policies and proposals intended to increase access to global medicines (those with a developed country market) by lowering prices, including: differential pricing; compulsory licensing; and donations. Finally, we consider policies aimed at encouraging the development of new medicines for neglected diseases (prevalent only in lower income countries) by reducing company born costs and risks and/or expanding the expected revenue for the manufacturer by increasing product demand. In particular, we describe "push" mechanisms that subsidize research inputs, and "pull" mechanisms that reward research output.

Some critics of subsidizing drug procurement and R&D contend that more cost-effective means of improving health status in developing nations may be through low tech, low cost health measures (e.g., mosquito bed nets, improved water supply) and non-health policy measures (reduction of developed country farm subsidies, investment in education) (Attaran, 2004). Without denying a role for these other tools and policies, the evidence suggests that medicines must be part of the solution as well. Several recent analyses stress the health burden due to high priority diseases (both infectious and communicable) for which medicines and vaccines serve as cost-effective treatments (CMH, 2001; Jamison, 2006; Barninghausen et al., 2008; Jamison, Jha and Bloom, 2009) with one study concluding that subsidizing R&D for neglected diseases was likely to be a cost-effective way of achieving health gain (Gray et al., 2006).

While this paper will focus on R&D effort and affordability issues primarily related to ex-manufacturer[2] drug prices, access to medicines also requires improving health care infrastructure to ensure that safe and effective products physically get to patients without mark ups that prohibit access (CGD, 2007; Levine et al., 2008).[3] Alongside the developments in product development and introduction, donors and global health agencies have placed more attention on the critical role that regulators, retailers, distributors and wholesalers have on product quality, availability and price. New funding for products combined with weak regulatory systems and weak information systems can contribute to a high level of counterfeit medicines in developing countries. WHO analyses suggest that the global share of counterfeit medicines is roughly 10%, but may be upwards of 40% in some developing countries (WHO-IMPACT, 2006; Rollings, 2007). These and other supply chain quality risks contribute to multinational pharmaceutical manufacturer reticence to participate in these markets (Levine, 2007; Yadav et al., 2007; Ballou-Aares, 2008).

[2] Ex-manufacturer drug prices are prices prior to any wholesaler, retailer and tax mark ups.

[3] Many therapies require administration and oversight by health care personnel, in order to mitigate the build-up of drug resistance, others require a network (especially of refrigeration) to maintain product quality.

2. Disease Burden

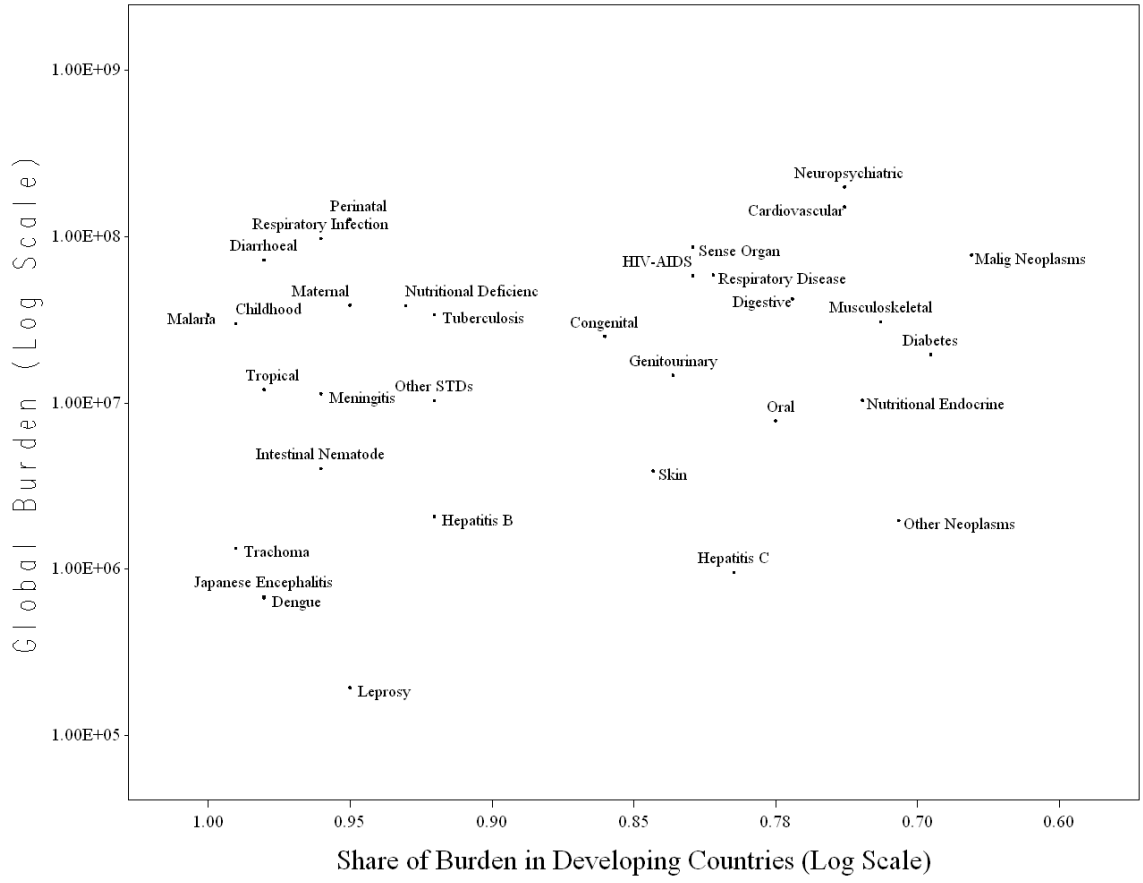
The World Health Organization disease classification divides diseases into three broad categories on the basis of global burden and share of burden concentrated in the developing world (CMH, 2001; WHO, 2006) as illustrated in Figure 1.

- Type I "global" diseases appear on the right side of Figure 1 and include cardiovascular disease, diabetes, cancer and other disease categories prevalent in both rich and poor countries (Reddy, 2004; Greenberg, Raymond and Leeder, 2005; Yach et al., 2006). The size of the expected markets creates necessary incentives to companies to invest in the development of new treatments but price often prohibits uptake in developing countries. Evidence that research responds primarily to demand in developed countries, particularly demand in patent-protected developed countries, was found by Kyle and McGahan (2009) using evidence on drug development changes after the 1994 Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). Research effort is less sensitive to demand in developing countries, regardless of whether those countries have patent protection (Kyle, 2008).

- Type II diseases, which appear in the middle and left side of Figure 1, are "neglected diseases". Those on the top of Figure 1, such as HIV/AIDS, tuberculosis and malaria, impart the largest burdens in terms of morbidity and mortality and while they may be present in both rich and poor countries, burden is disproportionately concentrated in the poorest countries. There has been some R&D over the past two decades in Type II diseases, but funding and effort has been concentrated in HIV. Furthermore, to the extent companies perceive an incentive to fund R&D, they tend to concentrate on product formulations and profiles that reflect the needs of patients and health systems of the developed rather than the developing countries. For example, health impact in developing countries depends upon product variations such as shorter treatment regimens, paediatric as well as adult formulations, point of care diagnostics and a focus on prevention relative to treatment but from the companies' perspective, this is not where the money currently is.

- Type III diseases, appearing on the far left of Figure 1, are referred to as the "very neglected diseases," they appear overwhelmingly or exclusively in developing countries and are the least commercially attractive (and thus, historically, have received the least R&D funding). This category includes tropical parasitic diseases such as leishmaniasis, schistosomiasis, and trypanosomiasis, and intestinal nematode infections such as ascariasis, trichuriasis, and hookworm. Diarrheal diseases are also included here. Despite a disease burden that exceeds that of malaria, R&D funding for diarrheal diseases is less than one third of R&D funding for malaria (Table 1).

Figure 1: Disease Burden: Disability-adjusted life years lost in low- and lower-middle-income countries relative to the rest of the world



Source: Authors' calculations using 2004 World Health Organization data on standard disability-adjusted life years (3% discounting and age weights). Poor and lower-middle income countries are classified according to World Bank definitions.

Table 1: Research and Development Funding by Disease in 2007, 2008 and 2009 in Nominal Dollars

2009 Rank	Disease	FY2007 R&D US$ (000)	FY2008 R&D US$ (000)	FY2009 R&D US$ (000)	2007%	2008%	2009%
1	HIV/AIDS	$ 1,083,018	$ 1,215,842	$1,168,029	42.3	39.4	35.7
2	Malaria	$ 468,449	$ 565,986	$602,396	18.3	18.3	18.6
3	Tuberculosis	$ 410,429	$ 467,539	$579,139	16	15.1	17.6
4	Diarrhoeal Diseases	$ 113,889	$ 138,160	$184,975	4.4	4.5	5.7
5	Dengue	$ 82,014	$ 132,471	$171,340	3.2	4.3	5.2
6	Kinetoplastids	$ 125,123	$ 145,677	$164,258	4.9	4.7	5.1
7	Helminths(Worms and Flukes)	$ 51,592	$ 69,518	$81,403	2	2.3	2.5
8	Bacterial Pneumonia and Meningitis	$ 32,517	$ 96,072	$69,616	1.3	3.1	2.2
9	Salmonella Infections	$ 9,117	$ 41,079	$40,292	0.4	1.3	1.2
10	Leprosy	$ 5,619	$ 10,073	$10,988	0.2	0.3	0.3
11	Rheumatic Fever	$ 1,670	$ 2,268	$3,084	0.1	0.1	0.1
12	Trachoma	$ 1,680	$ 2,225	$1,841	0.1	0.1	0.1
13	Buruli Ulcer	$ 2,413	$ 2,140	$1,879	0.1	0.1	0.1
14	Platform Technologies	$ 9,997	$ 16,570	$22,802	0.4	0.6	0.7
15	Core Funding	$ 110,922	$ 110,403	$74,381	4.3	3.4	2.3
16	Unspecified	$ 51,619	$ 78,180	$88,144	2	2.5	2.7
	Total	**$ 2,560,069**	**$ 3,094,202**	**$3,304,862**	**100**	**100**	**100**

Source: Moran, M. et al. (2011)

3. The economics of securing access to existing and future medicines

We turn initially to economic developments and policy issues most pertinent for Type I diseases and some Type II diseases like HIV and pneumonia, where products exist and are available in developed and some high-middle income countries but are often not available and/or not affordable in low-middle and low income countries. For the rest of Type II and Type III diseases, public and philanthropic funders and policy makers have opportunities through their support of product development, to influence the design and price of the product before it gets to market. But once approved, they have less opportunity to use the companies' developed world markets as a lever to negotiate better access for the poorest and need to rely either on company philanthropy in the form of donations or donor supported procurement to address any remaining affordability issues.

3.1 Increased Pharmaceutical Industry interest in MLICs

While the diseases of the poor are a low priority, many MNCs are looking to expand in MLIC markets to grow the sales of their products. Sales to Asian, African, and Australian markets doubled between 2004 and 2009 and Latin America experienced similarly robust growth (Figure 2). Pharmaceutical manufacturers are cutting jobs in developed countries and adding jobs in emerging markets (Loftus, 2010; Goldstein, 2009). In some cases, as in India, the companies are looking to tap into the recent growth in income levels that will likely translate into more out-of-pocket spending on pharmaceuticals as well as other health products. In other MLICs, economic growth is coupled with the expansion of state run insurance programs (as in China via new rural and urban worker and resident social health insurance programmes) (Zhou et al., 2008; Wagstaff et al., 2009; Cavanagh, 2010).

A number of factors have bolstered company interest in the emerging markets above and beyond rapid growth rates of per capita income. This list includes but is not limited to: improving macroeconomic stability; stronger IP protection thanks to patent and trade reforms through TRIPs and individual country trade agreements; improvements in health care delivery systems; and the pressure of expiring patents in developed markets, forcing companies to seek new opportunities (Riahi, 2002; Sehgal, 2002; Vilela, 2002; BMI, 2010; Cavanagh, 2010).

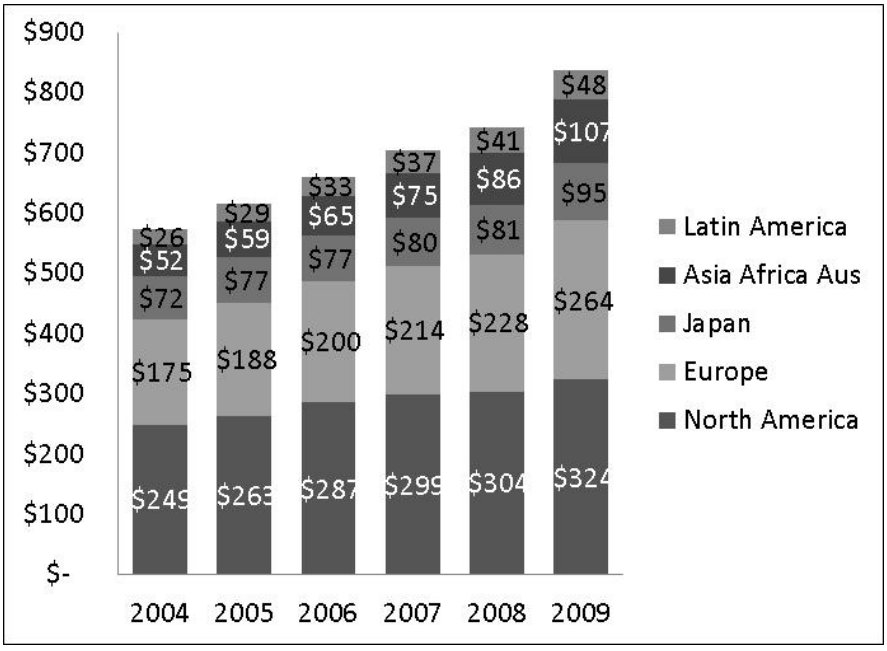
Multinationals are increasing their presence in emerging markets via acquisition, joint ventures, alliances and venture capital participation with local companies (BMI, 2010; Cavanagh, 2010). Table 2 highlights some recent activity in India. However, they are still struggling to identify appropriate business models for MLICs given that most of the population often have limited access to third party payer led insurance and are not able to pay high prices out-of-pocket. Success will likely require a shift from the companies' traditional model of supplying small volumes at high prices to the high income part of the population. As we show below, tools and models companies and partners are developing to address access issues for the poorest may

prove to be important training opportunity for companies as they think about broader expansion in MLICs.

Small and medium local companies are also growing in MLIC countries, notably India, China, Cuba, South Africa, and Brazil. In some cases, these companies are developing products for neglected diseases (Frew, Liu and Singer, 2009). Successful models for companies in developing countries include the generics industry, in which Indian companies have become major global players by serving developed and developing country markets, and the global vaccines industry, in which Asian companies have also emerged as suppliers for global and regional contracts with international agencies.

Niche companies might benefit from facilitation by an independent organization which provides business support, access to venture capital, advocacy for funding, and networking (Frew, Liu and Singer, 2009). BIO Ventures for Global Health offers a similar service to help companies based in developed markets. While successful developing country manufacturers primarily compete in the commercial market locally and abroad, large subsidization programs (e.g. GAVI) have also served as important customers, in particular for Indian vaccine manufacturers.

Figure 2: Distribution of pharmaceutical sales across regions and over time (US$ Billions at constant exchange rates)



Source: IMS Health

Table 2: Select Acquisitions and Alliances in India

MNC	Seller or Partner	Deal Size / Type	Date
Abbott	Piramal Health care	$3.7 B. / Acquisition	June 2010
Daiichi Sankyo	Ranbaxy (34%)	$2.4 B./ Acquisition	June 2008
Mylan Labs	Matrix Labs (71.5%)	$736 M./ Acquisition	August 2008
Sanofi Aventis	Shantha Biotech	€550 M / Acquisition	July 2009
Fresnius SE	Dabur Pharma (73.3%)	$185 M. / Acquisition	April 2008
GSK	Dr. Reddy's	Alliance	July 2009
Pfizer	Aurobindo	Alliance	March 2009

3.2 The Role of Patent Protection in MLICs

For a number of economic and policy reasons, MLIC countries have historically limited the protections for IP. A divergence of economic interest between MLICs and MNCs was recognized in the WTO TRIPS (Trade Related Aspects of Intellectual Property Rights) agreement which made drug patent recognition a condition of membership of the WTO for all countries, including MLICs, with three provisos:

- only products patented after 2005 were covered, with existing medicines "grandfathered" into the new systems;
- the least developed nations were given an exemption from introducing patents until 2016;
- all countries (rich and poor) are allowed to use compulsory licensing in the circumstances of a "public health emergency."

In addition the Treaty permits individual countries to choose their own policies on international exhaustion (which prohibits parallel trade or resale of pharmaceuticals outside the original country market). It is therefore possible for high-income countries to prohibit parallel trade and many do. It also is possible, however, for countries receiving low prices to ban parallel exports, thus protecting themselves from losing the benefit of these low prices.

Critics argued that the TRIPS provisions would not be enough to prevent price increases once countries became TRIPs compliant (Lanjouw, 1998; Watal, 2000; Fink, 2001). These arguments make assumptions about patented drug prices and the price impact of generic competition, both of which we consider below. In countries such as India, the pre-TRIPs IP policies combined with other industry policies helped enable the development of an industry of companies that sold generic versions of medicines that were still on patent in developed countries. Arguably

these companies are now competing in global generic markets and some are trying to move upstream into the business of developing new products.

3.3 Market Segmentation and Differential pricing

The considerable R&D investment required to bring a pharmaceutical product to market (DiMasi, Hansen and Grabowski, 2003) is a sunk (and therefore fixed) cost which firms expect to recover. One solution to this fixed cost problem is Ramsey pricing (also known as "differential pricing" and "tiered pricing") whereby prices are kept low for low income market segments with high demand elasticity, and high prices designed to recover R&D costs are charged to high income market segments with lower demand elasticity (Danzon and Towse, 2003).

In theory, when there are significant disparities of income, differential pricing can therefore both increase returns to R&D (so stimulating more research) and expand overall access to medicines, particularly to lower income groups of patients or low income countries (Danzon and Towse, 2003). To do this, prices in relatively richer countries would exceed the marginal cost of production and distribution by enough, in aggregate, to cover the fixed costs of research and development while prices in lower-income countries would be set close to marginal costs. Table 3 indicates the nature of income differentials across countries.

Table 3: GNP per Capita, Spending and Health Outcomes (by Income Classification)

Development Category	Population (Millions)	Mean Annual GDP per capita ($US)	Total Annual Spending on Health* ($US)	Life Expectancy (years)	Infant Mortality (per 1000 live births)
Low Income Countries	956	$486	$27	59	77
Lower-Middle Income Countries	3,661	$1,879	$81	68	47
Upper-Middle Income Countries	941	$7,555	$488	71	20
High Income Countries	1,061	$38,327	$4,406	80	6

*Components include public domestic spending, private domestic spending and donor assistance.
Source: World Bank (World Development Indicators)

This approach is viable only if markets remain segmented, i.e., there is no significant leakage of prices, through the use of international reference pricing (whereby payers in high income countries set their prices by reference to the [lower] prices paid in low income countries) or the

movement of physical product (parallel trade) from low price markets to high price markets, undermining the higher prices in these markets (Danzon, 1998; Kyle, 2008).

One way to avoid "leakage" through price referencing is the use of confidential discounts (Danzon and Towse, 2003). Confidential discounts are the chief means through which U.S. managed-care purchasers negotiate lower prices. Discounts to low-income countries or market segments could be given as confidential rebates paid directly to the ultimate purchaser. Wholesalers are supplied at a common price or act as distribution agents who do not own the product. Confidentiality could eliminate the opportunity for other purchasers to demand similar rebates and prevent wholesalers or other parallel traders purchasing the product at the low price intended for low-income countries and then exporting it to higher-price countries. It could also prevent arbitrage between market segments within countries.

Transparency facilitates price comparisons and so undermines differential pricing (Kyle and Ridley, 2007). However, advocates for transparency contend that bulk negotiation and knowledge of transaction prices elsewhere will enable reduced prices to be negotiated more generally, promoting access and so increasing static efficiency and hence consumer welfare (albeit with some offsetting reductions in producer welfare). The World Health Organization (WHO) and Health Action International (HAI) are working to post international pharmaceutical price comparisons at different levels of the supply chain (ex-manufacturer, wholesale, retail) (Babar et al., 2007; Cameron et al., 2009). The key difference between advocates of transparency and of confidentiality is their view of the impact on incentives for R&D. The focus of those advocating transparency is short term (static) efficiency. If companies cannot, as a consequence, earn returns on R&D then they would argue that other mechanisms will be needed to incentivize or undertake R&D.

Differential Pricing Policy and Practice

Starting in the late 1990s, non-governmental organizations (NGOs), notably Médecins Sans Frontières and Oxfam, combined with HIV/AIDS activist groups, the World Health Organization, the Clinton Foundation and governments such as the U.K. Department for International Development to step up the pressure on companies to bring down the prices of ARVs for the poorest countries. Many companies responded by introducing a differential pricing system with discounts for the poorest countries. Companies have also employed technology transfer where they provide voluntary licenses to generics manufacturers in the expectation that these manufacturers will supply products at low prices.

In addition to HIV/AIDS, forms of differential pricing have been employed for contraceptives and vaccines (Yadav, 2010). NGOs continue to call for transparency so as to monitor how systematic the price differentiation is (Oxfam, 2007). Advocates of confidentiality counter that transparency limits pricing freedom and potentially restricts access to medicines. The motivation for companies to employ discounts will decline sharply if all the details about those discounts are made public and then used as a reference for other buyers outside the lowest

tiers. There are other tools to bring down prices for new medicines – the allowance for competition pre-patent expiry – but at the risk of long term investments in new R&D.

Intra-Country Differential Pricing

It is even more challenging to use differential prices within countries than between countries. Within-country market segmentation is more feasible if there are different health care purchasers acting on behalf of the income groups identified, or if these groups attend different health care facilities to receive their medicines. If, for example, public-sector payers targeting lower income groups can be distinguished from private-sector payers targeting higher income groups, differential pricing is more likely to evolve. While the potential value for revenue, access and even profit associated with intra-country differential pricing is increasingly recognized – the mechanisms available to enforce differential pricing to date are limited and uncertain (BVGH, 2008; PF3, 2009).

A variety of approaches have been attempted to segment markets within countries and provide differential pricing, as indicated in Table 4. Differential pricing within countries appears more viable when: (1) pharmaceutical companies deal with large purchasers rather than with individuals (although individual discount cards have been used with some success); (2) uniform list prices are posted with confidential discounts from the list price paid separately to purchasers; and (3) lower prices can be passed on to patients in self-pay or co-pay markets, rather than be captured by intermediaries.

Table 4: Price Discrimination Mechanisms in Developing Countries

Level of Price Discrimination	Characterization / Example	Advantages / Disadvantages
Individual	Novartis Gleevec "GIPAP" program offers full contribution, shared contribution (local governments, other payers share cost) and copay (individual shares cost) models depending on the geography and ability to pay of the patient.	Targeted subsidies (+) High transaction costs (-)
Institutional or Delivery Channel	Price may differ depending on whether payer is the public or private sector. Channels such as NGO clinic or specialized hospitals which attracts either wealthy or poor.	Potential to distribute on a relatively large scale (+) Monitoring costs to avoid arbitrage(-)
Brand (Dual Brand Strategy)	Original drug is marketed to wealthy segment, licensed generic/secondary brand targeted toward poor.	Potentially lower monitoring costs (+), but arbitrage still possible May rely on channel segmentation or provider segmentation (-)
Provider	Pharmacists select branded (high price) or licensed generic product (low price) depending on their subjective assessment of patient income in their market. Residents apply for rebate cards. Sanofi Aventis applied this strategy with anti-malarial ASAQ.	Flexible discrimination of market at provider level (+) Potential cannibalization of profits from high cost version may undermine program (-)

Service (Bundling products and services)	Drugs and diagnostics offered at as a package (e.g. insulin, diabetes medicines and glucose test sticks).	Prices hidden for each element of the package (+) Feasible for limited set of products (-) Complex/multi-party contracting (-)
Country	In cases of least developed countries in particular, select manufacturers have reduced price to a fraction of "developed world" prices on a country-wide basis. Examples include GSK and Gilead (program prices drugs based on GDP/capita and HIV prevalence).	Administrative efficiency (+) Ignores potential profitable segments that could cross-subsidize the poor or motivate R&D (-)

Sources: Gilead (2011), Novartis (2011), Seiter (2008), Vaitheeswaran (2010), authors' analysis

3.4 Subsidies for the Purchase of Existing Medicines [4]

Governments, foundations and multilateral institutions have rapidly increased funding over the last decade to support health in low- and middle-income nations. Between 2001 and 2008 health Official Development Assistance (ODA) from the G20 and multilaterals increased approximately by a factor of 2.5 from $7.6 billion to $26.4 billion (Kates et al., 2010). Some of this share has been directed toward programs which purchase medicines such as the U.S. President's Emergency Plan for AIDS Relief (PEPFAR)[5], the US President's Malaria Initiative (PMI), the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), and the Global Alliance for Vaccines and Immunization (GAVI).

Purchasing mechanisms are increasingly wielding monopsony power to reduce price for patented products, increasing procurement of generics when feasible, i.e., where patents have expired[6], and encouraging competition. In the case of GAVI, donors are looking to use their funds to accelerate the introduction of new products at affordable prices into developing countries. They also want to encourage more companies to enter the market as suppliers. GAVI's model works if MNCs consider the funds sufficient to support a global differential pricing strategy and if new entrants consider the funds secure and long-term enough to justify investments in the supply of a vaccine.

[4] An important consideration related to subsidization is which diseases or countries deserve special consideration either with regard to support for R&D or for programs which expand access. We discuss the basis for choice of diseases in the next section of the paper. In the GAVI case, in terms of countries, if donors decide to stick to the $1000 per capita ceiling for entitlement (or indeed to reduce it in the face of limited funds) then rapidly growing economies like China and India will no longer be eligible for donor subsidies and greater engagement by their own governments will be required to meet the health needs of their poor populations.

[5] PEPFAR, the cornerstone of the US President's Global Health Initiative (GHI) (initially $63 billion over 6 years and then reauthorized with an additional $48 billion in 2009 out to 2014), accounts for approximately three-quarters of the GHI (Kates, 2010). Purchase of medicines is one piece of a much broader set of PEPFAR program objectives; in 2009, PEPFAR spent $425 million on ARVs out of a budget above $6 billion (PEPFAR, 2010).

[6] For example, the share of expenditures directed toward generics in the PEPFAR program has shifted from 9% in 2005 to 76% in 2008 (Holmes et al., 2010).

Programs such as the Affordable Medicines Facility for Malaria (AMFm) (discussed in the next section) and the Advanced Market Commitment for pneumococcal vaccines (AMC), (discussed in Section 4), indicate that it is possible for funders to employ strategic subsidies to bring down price and increase supply. That said, the impact of the financial crisis since 2008 combined with the introduction of new, more expensive vaccines for rotavirus, HPV and pneumococcal disease, is seriously challenging the GAVI (and UNITAID and GFATM) model. The demand for funds is growing at the time when the supply of aid funds from donors declines.

AMFm - The ACT Subsidy

One novel subsidization effort proposed by economist Kenneth Arrow, the Affordable Medicines Facility-Malaria (AMFm), uses a subsidy to the manufacturer of artemisinin combination therapies (ACTs) to reduce them towards the relatively cheaper price of the less effective mono-therapies and thereby attempt to slow the rise of resistance to artemisinin. Through the AMFm the ACT is supplied through existing distribution systems (both public and private) (Arrow, Panosian and Gelband, 2004; Laxminarayan, Over and Smith, 2006; Laxminarayan and Gelband, 2009; Laxminarayan et al., 2010).

A manufacturer targeted instrument works only to the extent that the manufacturer controls the final price or that the distribution system is sufficiently competitive such that mark-ups do not undo the impact of the subsidy. Research to date in developing country settings is mixed, but generally confirms that concentration among distributors, wholesalers and/or retailers and prices (or mark-ups) are positively correlated (Goodman et al., 2009; Patouillard, Hanson and Goodman, 2010). However, in this case of ATCs, patients cannot tell the difference between monotherapy and combination therapy in terms of benefit to them and so there is no medical basis for retailers to mark up the ACT relative to the monotherapy if both products are supplied to them at comparable prices. According to a pilot study in Tanzania, the subsidy at the top of the private sector supply chain can significantly increase usage of ACTs and reduce their retail price at the level of common monotherapies. In the study, people in the districts where the subsidy was introduced increased their use of ACTs from 1% to 44% in one year (Sabot et al., 2009).

3.5 Donations

Donations of product are another tool that companies can and do employ to improve product access. The International Federation for Pharmaceutical Manufacturers Association (IFPMA) provides an up to date database of company donation programs to developing countries. One of the first is Merck's donation of Mectizan (ivermectin) for the treatment of worms. Originally developed for the veterinary market (worms in dogs and cats), Merck partnered with TDR of the WHO to develop a version for humans and began donating it to Africa first for the treatment of onchoceriasis (River Blindness) in 1987, and from 1998, also for lymphatic filariasis. As of 2010, more than 700 million people had been treated with ivermectin (IFPMA, 2010). In Africa and Yemen, ivermectin is co-administered with albendazole, donated by GSK.

The donation and distribution of these therapies involves a global public-private partnership of United Nations agencies, governmental and nongovernmental organizations, local communities, and the private sector. In October 2010, at the launch of WHO's First Report on Neglected Tropical Diseases, a number of companies including GSK, Eisai, Johnson & Johnson, Sanofi-Aventis and Novartis announced increased commitments to their current donation programs.

Critics of donation programs have two concerns. Firstly, donation programs are only good as long as the company involved is willing to continue donating the product and therefore are not necessarily a sustainable solution to the problem – be that of supply or affordability or both. Secondly, donating, in theory at least, could crowd-out generic competitors who cannot compete with "free" (Oxfam, 2007). Donation programs need to have a long term strategy for sustainability, so that the immediate benefits are not offset by any later disruption to supply.

3.6. Flexibility in patent rules to improve access

A number of NGOs and academics have made proposals and advocated that governments use stronger IP rules and tools to secure access to medicines for the poorest. Three are provided below. All three have in common the fundamental premise that companies should forgo patent rights in select poor countries to promote access. They assume that innovators' incentives to develop new therapies are minimally affected by their ability to patent in the poorest countries and that generic companies would enter these poor markets with adequate quality generic copies as soon as the patents are no longer enforced.

(1) The country is poor and the product is deemed "essential". Médecins Sans Frontières (MSF, 2008) and others have advocated the countries make better and more frequent use of the compulsory license TRIPs provision that allows governments to ignore patent rights when there is a national health emergency[7]. Such national emergencies might include public health crises, including those relating to HIV/AIDS, tuberculosis, malaria, and other epidemics;

(2) The country is poor and there is a lucrative market elsewhere. Lanjouw (2006) proposed that developers have patent rights either in rich countries or in poor countries, but not in both. Developers selling in rich countries would agree not to enforce patent rights in poor countries (countries that constitute two percent or less of global sales value). In those poor countries, other companies could manufacture and sell generics without licenses. In the remaining countries, normal TRIPS rules would apply. It would have an impact, for example, on hypertension, where a large number of poor countries would constitute only 2% of sales, but not for malaria, however, where much of the global sales are in poor countries.

[7] Although in this case the government might agree to pay a royalty fee for the patent owner.

(3) The international community "buys out" the patent. Manufacturers could give up patent rights in return for fair compensation from governments. This is linked conceptually to recent proposals for prizes, which we discuss below. Participation in a patent buyout could be required or voluntary (Kremer, 1998). Banerjee, Hollis and Pogge (2010) propose that manufacturers that set prices equal to manufacturing costs could receive cash from a Health Impact Fund for up to 10 years. The share of the fund paid to a given manufacturer would depend on the net health impact of the product. The fund would be created by contributions from governments and foundations. The amount of funding for a given drug would not be specified in advance but would depend on use of the drug and evidence of realized benefits. The lack of specificity would provide flexibility in adapting to new innovations and needs. It would concern manufacturers, however, by introducing the possibility of opportunistic behaviour on the part of the Fund's administrators (DiMasi and Grabowski, 2004).

3.7. Increasing Generic Competition

In most MLICs generics versions of originator drugs are available. Whether drug prices are affordable in MLICs in part depends on the prices of generics. There is often an implicit assumption that generics are always low price. Empirical work by Danzon, Mulcahy and Towse (2011) analyzing determinants of ex-manufacturer prices for originator and generic drugs to treat HIV/AIDS, TB and malaria in MLICs found that although there were multiple originator and generic competitors in most MLIC country/classes, competition from generics was not effective at reducing prices in self-pay retail pharmacy channels. Because generics are not required by regulation to meet high quality standards, quality uncertainty led to branded generics that compete on brand name rather than price.

They found, however, that pooled procurement mechanisms achieved significantly lower originator and generic prices. For originators, this may reflect greater willingness to grant discounts to a distribution channel that reduces risks of price spillovers to richer purchasers in the same country and to other countries. For generics, procurement attracted multinational generic suppliers that meet quality standards, and have scale advantages over the local branded generics that dominate the retail pharmacy channels.

Empirical evidence suggests that better mechanisms are needed to promote price competition and enable differential pricing between and within low and middle income countries and that third party procurement or the use of other protected channels may offer a route forward.

4. The economics for securing R&D

4.1 R&D Output for Neglected and Very Neglected Diseases

Insufficient demand (too little spent on health care and pharmaceutical in particular by patients in developing countries) combined with high scientific and process (regulatory systems, trial sites) risks and costs has explained the dearth of public and private R&D spending for Type II

and III diseases (Table 5) (Frick, Keuffel and Bowman, 2001; Shah, 2002; Onwujekwe, Hanson and Fox-Rushby, 2004; Weiner, 2002; Dolgin, 2010). Simply stated, product development was not commercially viable despite the significant health burden associated with these diseases.

The low absolute levels of R&D and new products for these diseases are well document. Pecoul et al. (1999) found 13 of 1450 NCEs developed between 1972 and 1997 directed toward neglected diseases. Trouiller et al. (2002) reported that from 1975-1999 just 16 of 1393 new chemical entities (NCEs) were registered for tropical diseases[8] or tuberculosis. Many of these products came out of research intended for oncology or veterinary markets (Ridley, 2003), all received public support and many were developed in partnership with the WHO's TDR (Special Programme for Research and Training in Tropical Diseases) (Troullliller et al., 2002; Ridley, 2003).

Evidence suggests that in the period since 2000, and the establishment of product development partnerships, the amount of public, private, funding and the number of products has increased. The annual rate of new product approvals for neglected diseases and very neglected diseases grew from 1.8 in 1975-1999 to 2.6 in 2000-2009 (Cohen, 2009). Between 2000-2009, 26 drugs and vaccines for neglected and very neglected diseases received worldwide marketing approval (Cohen, 2009). Research output remains low, however, relative to disease burden and relative to Type I diseases.

4.2 R&D Initiatives and Incentives for MNCs

The question as to whether companies and their investors are simply "missing" a profitable opportunity because of the lack of good information about the neglected disease markets has prompted a number of organizations to try and generate market assessments, especially for Type II diseases, such as TB and Pneumococcal vaccine, prevalent in middle as well as low income countries (Rouse, 2001; BVGH, 2006). While methodologies vary considerably, the TB drug and vaccine studies indicate close to $500m per annum markets but also sizeable regulatory, political and logistical challenges to securing these markets.

Multinational companies are committing more resources towards neglected disease R&D including the establishment of dedicated research facilities (GSK's Tres Cantos, Spain; Novartis's Institute for Tropical Disease in Singapore and Vaccine Institute for Global Health in Sienna Italy; Astra Zeneca's TB Facility in Bangalore, India; Merck's Hilleman Research Lab [in partnership with the Wellcome Trust] in India), but relatively little of the cost of these projects is funded out of the companies' commercial budgets. External funds and partnerships play a critical role in funding and supporting these initiatives.

[8] For the purposes of analysis, "tropical diseases" included parasitic disease (malaria, African trypanosomiasis, Chagas' disease, schistosomiasis, leishmaniasis, lymphatic filariasis, onchocerciasis, and intestinal nematode infections), leprosy, dengue, Japanese encephalitis, trachoma, and infectious diarrhoeal disease.

Global health funders can leverage and magnify the commercial value of these opportunities through the design of incentives and funding initiatives. Companies will require funding support to take the decision to work on Type II and III diseases but how much and in what form varies by disease and by company. In theory, the greater the actual market, the lower the required public or philanthropic subsidy.

4.3 Push and Pull Incentives with Government and Donor Funding

Several organizations and researchers have examined mechanisms for funding and prioritization of R&D (CMH, 2001; GFHR, 2002; Towse and Kettler, 2005a; Hecht, Wilson and Palriwala, 2009; WHO, 2010). Appropriate subsidies for these neglected diseases ideally correct for the lack of incentives that the small markets create by tipping the risk return ratio in favour of new research, development and delivery (Zeckhauser, 2002). Jena, Mechoulan, and Philipson (2011) estimated that the "private market provides insufficient spending for research and development, possibly under-providing R&D by as much as 60 percent if one accounts for the benefits of altruism."

Mechanisms designed to encourage companies to undertake R&D on neglected diseases are generally characterized as either “push” programs which support inputs into research or “pull” programs which pay for outcomes or outputs of research (Kettler, 2000; Kremer, 2002; BVGH, 2009; Hecht, Wilson and Palriwala, 2009). In terms of simple economics, push mechanisms shift the supply curve down by reducing the cost of R&D through direct grants, technical assistance or tax breaks. Pull mechanisms shift the demand curve up and out by rewarding successful product development with higher prices and/or more volume. Push mechanisms include direct grants for R&D (e.g., from the US NIH), tax credits for R&D and fast-track approval for the neglected disease product (i.e., time saving measures). Pull mechanisms include purchase commitments, tax credits for sales of developed products for high priority indications, market exclusivity rights, patent extension rights transferable to other medicines, priority review vouchers (where companies are rewarded for their neglected disease efforts with a priority review for another product of their choosing), research tournaments, prizes and signaling via reimbursement for related products (Kettler, 2000; Kremer, 2000; WHO, 2008).

A key distinction between push and pull is whether the reward is conditional on successful product development. Pull funding is contingent on success. Push funding reduces the cost or risk to the product developer but is not contingent on success.

4.3.1. Push Incentives

Product development partnerships (PDPs)

The dominant push mechanism in global health is the product development partnership (PDP) where donors fund the initiative and the initiative, in turn, evaluates, funds, helps manage and support projects underway in research institutes, universities, companies or some combination. While the structure of the contract varies, the PDP tends to fund the product developer on a stage by stage basis with each partner retaining the option to drop out at the end of any stage.

In exchange for the funds, the product developer agrees to global access agreements to help ensure that any successful product that results from their partnership reaches the intended patients. The access agreements speak to price as well as supply commitments. Donors carry most of the risk of failures because they pay up-front rather than upon receipt of the product. And as was noted above, how much needs to be donor funded will depend on the company, product and disease. A diagnostic company may seek less research support to work in TB but still require/look to the PDP to provide technical assistance and marketing support. An emerging vaccine company may require funding and technical support to complete product development but find the market sufficient to invest their own resources in manufacturing and distribution.

Many PDPs emerged during the late 1990s and early 2000s, and typically consist of a non-profit organization or "virtual" company that partners with industry, governments, funders and other organizations to develop a portfolio of medicines, vaccines or products for use in the treatment of neglected diseases (Kettler and Towse, 2002; Matlin et al., 2008). By one count, there are as many as 24 PDPs (Matlin et al., 2008). These include the Medicines for Malaria Venture (MMV), International AIDS Vaccine Initiative (IAVI), World Health Organization Special Programme for Research and Training in Tropical Diseases (WHO/TDR), Institute for One World Health (iOWH), Drugs for Neglected Diseases initiative (DNDi) and the Infectious Disease Research Institute (IDRI). Leading donors for PDPs include the Bill and Melinda Gates Foundation (BMGF), the United States (USAID), the United Kingdom (Department for International Development [DFID]) and the Dutch Ministry of Foreign Affairs (Moran et al., 2011) with the BMGF providing more than 50% of the funds.

Most PDPs manage a portfolio of products across a range of development phases, although frequently PDPs focus on a particular therapeutic category. It is still too early to credibly gauge PDP productivity in terms of final products, but we can note that despite their relative novelty, over 85% of products in development by 2008 for neglected diseases are associated with PDPs (Matlin et al., 2008) and PATH, FIND, MMV, DNDI, and the IOWH have all successfully launched new products in the past few years – a meningitis vaccine, TB diagnostic, paediatric formulations for an anti-malarial, a new ACT combination for malaria and a leishmaniasis drug, respectively. All have a range of partnerships with MNCs and biotechnology companies; IFPMA's partnership data base highlights close to 50 examples of MNCs working on product development with PDPs.

Table 5: Finance for Product Development Partnerships ($US, 2008)

By Funding Source			By Disease			By Recipient		
Source[9]	**Amount**	**Share**	**Disease**[10]	**Amount**	**Share**	**Recipient**[11]	**Amount**	**Share**
Philanthropic	$386,384,877	0.67	HIV/AIDS	$149,942,311	0.26	IAVI	$86,598,877	0.15
BMGF	$351,426,806	0.61	Malaria	$147,384,105	0.25	MMV	$46,030,613	0.08
Other	$34,958,071	0.06	Tuberculosis	$124,855,766	0.22	WHO/TDR	$37,039,883	0.06
Governments	$188,068,613	0.32	Kinetoplastids	$37,090,486	0.06	iOWH	$28,409,973	0.05
US	$54,985,749	0.09	Diarrheah	$35,182,635	0.06	DNDi	$22,439,420	0.04
UK	$28,094,078	0.05	Multiple	$31,584,161	0.05	Sabin Institute	$14,527,320	0.03
Netherlands	$19,807,167	0.03	Dengue	$20,537,201	0.04	IDRI	$14,340,927	0.02
Canada	$16,244,572	0.03	Helminths	$19,437,208	0.03	EVI	$4,398,781	0.01
Spain	$13,116,473	0.02	BPM	$10,115,660	0.02	Other	$326,298,494	0.56
Other	$55,820,574	0.10	Delivery	$2,842,936	0.00			
Private Sector[12]	$5,630,798	0.01	Leprosy	$526,586	0.00			
			Salmonella	$369,793	0.00			
			Other R&D	$215,440	0.00			
Total	**$580,084,382**	**1.00**	**Total**	**$580,084,382**	**1.00**	**Total**	**$580,084,382**	**1.00**

Source: Moran, M. et al. (2009) (G-Finder Database)

[9] BMGF=Bill and Melinda Gates Foundation

[10] Multiple=Core funding of a multi-disease R&D organization, BPM=Bacterial Pneumonia & Meningitis, Delivery=Delivery Technologies and Devices

[11] IAVI=International AIDS Vaccine Initiative, MMV=Medicines for Malaria Venture, WHO/TDR=World Health Organization: Special Programme for Research and Training in Tropical Diseases, iOWH=Institute for One World Health, DNDi=Drugs for Neglected Diseases initiative, IDRI=Infectious Disease Research Institute, EVI=European Vaccine Initiative

[12] Private sector may also commit in-kind resources such as R&D facilities or personnel rather than direct investment into a PDP initiative. Additionally these figures are based on survey data. Both factors potentially bias the estimate.

Patent Pools

Patent pools are collections of patents contributed by IP holders for use by qualified users or other members in the pool. Members agree to use a set of patents as if pool members owned them jointly and to license them as a package to other firms or organizations. Patent pools have partial exclusivity, restricting use outside the pool but allowing use inside the pool. Pools reduce litigation risks and lower license fees and transactions costs for members and others qualified to access the patents.

While not patent pools in the technical sense – where members jointly own and work on patents together – a number of new initiatives designed to expand access to patents and "know-how" as a means to promote R&D and supply have adopted the title. One example is the Pool for Open Innovation, founded by GSK in 2009 and operated by BVGH. In this case, companies are encouraged to contribute patents and affiliated programs with the goal of making it easier for others to build on the companies' research, successes and failures through their access to donated enabling technologies and data, including data on failures (Dentzer, 2009). The Pool for Open Innovation restricts licensing to efforts related to the 16 "neglected tropical diseases" as defined by the FDA (this list excludes HIV/AIDS) and any activity using the patents can only occur in the UN's 49 Least Developed Countries.

In contrast, the UNITAID-supported effort, the Medicines Patent Pool, targets HIV exclusively. It seeks to gain access to companies' ARV therapy patents with the goal of increasing supply and of enabling the development of fixed dose combinations and paediatric formulations by other companies (UNITAID, 2010). Participating IP contributors would be granted some royalty but how the value will be determined is not clear and likely to be highly contestable. The geographic scope of the initiative is also still under discussion – i.e., will companies be free to use the pool's patents only for the patients in the low income countries or also for patients in middle income countries. As such the likelihood that such pools will generate significant entry is limited if rights by the originator to subsequent commercialization is restricted.

As pools are a relatively recent development (generally established since 2009), it is not clear the degree to which these initiatives will result in significant advances in either development or access to medicines. While it can address the concern that MNCs may otherwise hang on to patents rights that they cannot commercially exploit, and also provides an outlet for new research by MNCs, product development costs still need to be met by someone.

4.3.2. Pull mechanisms

Whereas a push mechanism subsidizes research inputs, a pull mechanism rewards research output. A pull mechanism only provides payment if the developer meets a goal. The goal might be vaccine development, manufacturing, or access. Towse and Kettler (2005b) suggest that pull mechanisms for treatment of neglected diseases are successful when they are designed to: (1) motivate new research without wasting resources; (2) specify which treatments are eligible; (3) be credible in eyes of developers; (4) handle follow-on drugs; and (5) ensure the products get used by patients.

Advance market commitment

Advanced market commitments are pull mechanisms in which donors encourage development of vaccines and other treatments by guaranteeing a specified price for up to a certain volume (Kremer and Glennerster, 2004; Berndt et al., 2007). Donors provide funding for the top-up on the price of the product above what the buyer will pay in the long term, and specify the disease, product characteristics, and price in advance. By increasing prices, an advance market commitment can improve the value of the developing market relative to the developed market such that companies make a decision to enter the former as well as the latter.

To motivate companies to spend their own funds to develop products for a neglected disease, the AMC must be credible and the market offered must be sufficiently large (Levine, Kremer and Albright, 2005). Payment is made only when a product is developed, approved and the patients indicate a willingness to buy it; so the developer bears the technical and the demand risk. Donors cover the bulk of the price with the end user making a co-payment. The co-payment helps insure that a new product meets a market test. The price subsidy expires when the AMC guarantee is exhausted. After the funds expire, participating companies must supply the product or vaccine at low and sustainable prices, ideally at the level of the co-payment that the user is able to afford but more likely at a level that still requires some donor subsidies.

Pull mechanisms need to specify how second and later entrants are rewarded. The AMC handles this problem better than many pull mechanisms, because fast followers can capture some of the funds provided that either (a) entry occurs sufficiently soon after the first entrant that funds are still available or (b) donors take the decision to reserve some funds to guarantee prices for later entrants with the explicit goal of bringing more than one company in to the market.

Towse and Kettler's fifth criterion was that patients must get access to the new product. Again, the advance market commitment handles this concern better than many pull mechanisms because payment is based on utilization. After the AMC fund is exhausted, the participating suppliers commit to supply at an agreed "tail" price. Less clear is whether the market created by the AMC (demand for the vaccine at the tail price) will serve as a sufficient draw to additional suppliers to enter once the AMC funds have been allocated.

The AMC has flaws that are characteristic of many pull mechanisms. If the payment is excessive, i.e., donors pay more in the form of a subsidy than needed to pull in the company, then resources are wasted, although higher prices are likely to get products to the market more quickly – something that can also be accomplished by a higher initial premium (Kremer et al., 2005). One way proposed to address this risk is for companies to bid on the reward they would want if they were successful in taking a pre-clinical candidate through human trials. The funder could construct an AMC around the lowest bid, although arrangements would be needed to cover development failures and follow-on entry. While interesting in theory, it is unclear that such a scheme could be put in to practice.

Because clinical development takes many years, AMCs targeted at pulling forward early stage candidates will be announced well in advance of a successful product. It is challenging to specify this far in advance the target product profile and set a price. This time lag could favour developers and lead to the possibility of "agency capture"; if no company responds to the initial offer or respondents are struggling to make progress, donors will be under pressure to relax the definition of what qualifies or to increase the price (Farlow et al., 2005). As the lag between design and approval increases, so too does the opportunity cost of capital and so the necessary price. Even advocates of the AMC suggest it might be cheaper and more effective to start with push funding for early stage products and reserve pull mechanisms for later stage products (Farlow et al., 2005).

In 2010 the first AMC was launched, to speed introduction of a pneumococcal vaccine to developing countries by encouraging companies to increase their global supply. The AMC requires eligible companies seeking the price premium to supply product to GAVI-eligible countries at a price below the developed world price but higher than a local price countries could pay out of their own resources. Five countries and the BMGF committed U.S. $1.5 billion. Both Pfizer and GSK have a vaccine that the AMC Independent Adjudication Committee has deemed eligible for AMC funds and both have been introduced in a GAVI country, Pfizer's in Nicaragua and GSK's in Kenya.

Priority review vouchers

In 2007, the US passed into law a priority review voucher (PRV) system where the developer of a treatment for a developing country neglected disease (such as malaria or leishmaniasis) receives a voucher for priority review from the Food and Drug Administration (FDA) to be used with a product of their choice or sold to another developer. The proposal for the voucher was published in 2006 (Ridley, Grabowski and Moe, 2006) and sponsored into U.S. law in 2007 by Senators Brownback and Brown.

Priority review means that the FDA aims to render a decision in six months. In contrast, the FDA aims to complete a standard review in about ten months, and it often takes even longer. The median difference in recent years is about seven months (Grabowski, Ridley and Moe, 2009). Top selling treatments can yield billions in sales each year, so being approved months earlier can be worth hundreds of millions of dollars to the voucher holder (Ridley, Grabowski and Moe, 2006; Grabowski, Ridley and Moe, 2009). About half of the blockbuster drugs in the 1990s received a standard review, and thus could have benefited from a PRV. The voucher's value derives from three factors: shifting sales earlier, longer effective patent life due to earlier entry, and competitive benefits from earlier entry vis-à-vis rivals. To redeem a voucher, the voucher holder must pay the FDA an additional user fee ($4,582,000 in 2011) and provide the agency with a one-year notice before redemption.

The PRV reduces two types of inefficiency. First, the voucher speeds approval of potential blockbuster therapies in the US, getting US patients access to these treatments more quickly. Second, the voucher motivates more treatments for neglected diseases, although it does not guarantee access to treatment in developing countries. Funding from governments or

foundations might be needed to purchase treatments for poor people. If the voucher is too generous (the rewards far exceed the cost of the additional research), or it rewards research that would have been conducted anyway, value diminishes. Novartis won the first voucher in 2009 for US approval of its malaria therapy Coartem (artemether/lumefantrine), a product that was already on the market in other countries. How Novartis uses the voucher will signal to the market its potential value. A PRV scheme has also been proposed for Europe (Ridley and Calles Sánchez, 2010).

Patent extensions

Whereas the PRV speeds a product to market, an alternative reward would be to extend a product's patent life. In the US, current law provides companies with a six month patent extension for developing paediatric formulations. Extending the patent of (say) a leishmaniasis drug would bring limited value to a company, but offering a six month extension for a product of their choice, and making that transferable voucher, could have great value (Kettler, 2000). In contrast to the PRV, a transferable patent extension voucher would be applied to a product that has been on the market for many years, so there would be greater certainty about the value of extended exclusivity and it can be applied at the point when a product has reached peak sales, increasing its value.

A problem with transferable patent extensions, however, is that they delay access to generic drugs, keeping prices high, and in effect taxing users of the drug receiving the patent extension to pay for neglected disease research. In the case of paediatric formulation patent extensions in the US, an FDA study determined that the additional cost of the policy was approximately $30 billion over 20 years with consumers footing 47% of the cost, generic firms losing 36% of the total and pharmacists (who typically charge more markup on generics) missing out on the remaining 17% (Kettler and Collins, 2002). Beneficiaries of the policy are clearly children who are prescribed (or would have been prescribed) the medicines on which additional studies were conducted. For the proposed transferable patent extension, developing countries would benefit while costs are borne by developed country consumers, generic firms and pharmacists. Patent extensions also have other problems familiar to pull mechanisms, in particular not ensuring that the neglected disease treatment that wins the reward actually reaches its targeted patients.

Prizes and "de-linking" the cost of R&D and the price of health products

One of the limitations of the PRV (and arguably the transferable patent extension idea) is that access agreements are not explicitly embedded in the legislation. The product developer is rewarded at the point of receiving FDA approval for a qualifying product but is not held accountable to a target product profile (is the product appropriate or affordable) or to participate in the product delivery process (does the product ever reach the intended patient?)

A recent review by Wilson and Palriwala (2010) found that various proposals have recently been put forward linked to the use of prizes as a pull incentive for product development, the most ambitious of which use the prize incentive as an alternative to patent protection. The prize reward is made contingent on the product developer making all the relevant IP available to competing manufacturers as a way to secure access (Love and Hubbard, 2007). Underlying

this proposal is the idea that the cost of R&D should be "de-linked" from the price of the product. Rather than earn monopoly rents through patents, the prize would pay the company back for any costs incurred in a single payment and the generic companies would be free to manufacturer from the day the product is approved. Proponents of the Health Impact Fund (Banerjee, Hollis and Pogge, 2010; Pogge and Hollis, 2008) put forward a different approach to achieve the desired innovation and health impact: a prize fund would again be used as the "draw" for innovation, but in this case the product is supplied at a generic price and the developer is not rewarded for the R&D element until it can demonstrate that the resulting product has health value for the intended patients, i.e., the rewards would be linked explicitly to health outcomes.

While the idea of de-linking R&D costs from the product price has attracted attention at WHO and elsewhere, how feasible it is to implement in practice has yet to be demonstrated (WHO, 2008). It is unclear if companies would respond and invest their own resources (or investors, theirs, in the case of biotechnology companies) against the potential promise of some or all of a prize fund, whether there would be sufficient markets to attract multiple suppliers as a way to compete the prices down, whether the prize specifications can be sufficiently detailed as to steer companies to the "right" technologies (Wilson and Palriwala, 2010). The promoters of the Health Impact Fund recognize, for example, that they need to practical answers to the question of how health impact would be "demonstrated" in practice, and how their model would deal with follow-on products.

4.4 Combining, and trading-off between, push and pull mechanisms

At its simplest, push approaches involve payment in advance and pull approaches involve payment only when a product successfully reaches a pre-specified milestone, be that regulatory approval or a decision by payers to buy. The way push and pull mechanisms work as incentives could have important differences in the resulting development costs and success rates.

Push efforts, at least in theory, should have lower cost per input in cases where non-profits are directing the work because they are able to negotiate preferential pricing for resources, staff, and contractors, as well as in-kind contributions from industry (Kettler, White and Joran, 2003; Moran, 2005).

Pull approaches, where companies are only rewarded for successes, means they are motivated to kill questionable projects early in an effort to avoid failures during the later, more expensive stages (Hsu and Schwartz, 2008). This could result in higher late stage success rates for pull driven work than push work though might also result in "overpruning" early, with some good but risky ideas being killed (a Type II error where companies underestimate the probability of success). With push approaches the developer might have an incentive to do the work even if it perceives a low chance of success, if it is getting paid for input. Under push, one might therefore expect to find more activity and larger portfolios of products, but lower success rates (Type 1 error where companies do not kill projects soon enough). PDPs are often evaluated on

how much they have in the pipeline rather than how good the products are and whether they kept to their budget forecasts. This can motivate PDPs to keep projects alive and spend money. Rather than be rewarded for "under spending" during the term of a grant, i.e., organizing the business to save money until promising projects come along, the PDP risks losing the money in "use it or lose it" arrangements.

A better understanding of relationship between incentive tool and product developer's behaviour would in theory allow funders and tool designers to modify and combine tools so as to minimize costs and maximize success rates and efficiency. In reality, designers have limited flexibility because of legislative processes, contract regulations, lack of information, and the need to send clear signals to companies planning R&D investments. Nonetheless, there are modifications that could be made to improve the reward structures within push mechanisms to improve performance and outcomes and to combine push and pull so as to improve success rates.

The US Orphan Drug Act of 1983 and subsequent Japanese (1993) and European (2003) orphan drug policies, are examples of push-pull combinations – in this case combinations of tools designed to encourage R&D for drugs to treat orphan diseases, defined as diseases affecting a pre-specified "small" number of patients in the Act's country. The US Orphan Drug Act combines a pull mechanism – seven years of marketing exclusivity upon FDA approval – with a number of push mechanisms – tax credits for up to half of their clinical testing expenses, tax credits for drugs requiring foreign testing when a sufficient testing population does not exist in the US, and modest grant and advisory support.

Most neglected diseases of the poor in developing countries also qualify for orphan status because of their low US prevalence, but there are limited US benefits from tackling them. Evidence suggests that the Orphan Drug Act works best for "rare but not too rare" diseases where companies can take full advantage of the exclusivity provision and offer high prices (Lichtenberg and Waldfogel, 2008; Yin, 2008). There are insufficient numbers of people to charge the high prices to for either "very rare" US based diseases or the neglected diseases of the global poor.

5. Conclusions

This paper details the approaches the pharmaceutical industry, governments and other stakeholders have employed (or advocated) to a) improve access to existing global medicines and b) motivate new R&D for neglected disease drugs and vaccines. Incentives in both areas have changed substantially over the last decade, in part because of a positive change in the public policy and financing environment among donor governments, international agencies and major private foundations. Differential pricing, donations, and voluntary and compulsory licensing can increase access to "global" medicines among poor patients. With differential pricing, MLIC markets are not necessarily unprofitable and will be a source of revenue growth for MNCs and regional companies. With the additional incentives from push and pull mechanisms, pharmaceutical firms have stronger incentives to develop medicines to treat

neglected diseases. Not surprisingly many NGOs and academics remain critical of the industry's performance and have proposed radical policy changes. Our view is that current and future initiatives should be based solidly on a mix of theory and empirical evidence; we have set out relevant theory and discussed existing evidence. As many programs aimed at improving R&D and access are relatively recent, future analyses of specific programs and initiatives will undoubtedly help us understand which policies and programs work well and which do not, and policy can be adjusted accordingly.

References

Agarwal, N. (2009) *Tuberculosis research & development: A critical analysis of funding trends, 2005–2007. An update.* New York: Treatment Action Group.

Alliance for Case Studies for Global Health. (2009) *Case studies for global health: Building relationships, sharing knowledge*. Available at www.casestudiesforglobalhealth.org [Accessed 27 May 2011].

AP (Associated Press). (2010) *MicuRx, Cumencor sign development deal with Pfizer.* 7 April. Available at http://www.businessweek.com/ap/financialnews/D9EUBI3O0.htm [Accessed 27 May 2011].

Arrow, K.J., Panosian, C. and Gelband, H. eds. (2004) *Saving lives, buying time: Economics of malaria drugs in an age of resistance*. Washington, D.C.: National Academy Press.

Attaran, A. (2004) How do patents and economic policies affect access to essential medicines in developing countries? *Health Affair*s. 23(3), 155-166.

Babar, Z.U.D. et al. (2007) Evaluating drug prices, availability, affordability, and price components: Implications for access to drugs in Malaysia. *PLoS Medicine.* 4(3), e82.

Ballou-Aares, D. et al. (2008) *Private sector role in health supply chains: Review of the role and potential for private sector engagement in developing country health supply chains.* Technical partner paper 13. [NP]: Dalberg Global Development Advisors, the MIT-Zaragoza International Logistics Program and the Rockefeller Foundation.

Banerjee, A., Hollis A. and Pogge, T. (2010) The Health Impact Fund: Incentives for improving access to medicines. *Lancet.* 375(9709), 166-169.

Barninghausen, T. et al. (2008) *The economic case for expanding vaccination coverage of children*. Copenhagen: Copenhagen Consensus Center.

Berndt, E.R. et al. (2007) Advance market commitments for vaccines against neglected diseases: estimating costs and effectiveness. *Health Economics.* 16(5), 491-511.

BMI (Business Monitor International). (2010) *India pharmaceuticals & health care report Q3 2010*. London: Business Monitor International.

BVGH (Bio Ventures for Global Health). (2006) *Tuberculosis vaccines: The case for investment*. Washington, D.C.: Bio Ventures for Global Health.

BVGH (Bio Ventures for Global Health). (2008) *Partnering for Global Health Forum 2008*. Washington, D.C. 10-12 March.

BVGH (Bio Ventures for Global Health). (2009) *Global health primer*. Washington, D.C.: Bio Ventures for Global Health. Available at http://www.bvgh.org/Biopharmaceutical-Solutions/Global-Health-Primer.aspx [Accessed 26 May 2011].

Cameron, A. et al. (2009) Medicine prices, availability, and affordability in 36 developing and middle-income countries: A secondary analysis. *Lancet.* 373(9659), 240-249.

Cavanagh, J. (2010) *Research and Markets: Opportunities in emerging pharma markets: Strategies for optimizing growth in key regions and therapeutic areas*. Dublin: Business Wire.

CGD (Center for Global Development). (2007) *A risky business: Saving money and improving global health through better demand forecasts*. Washington, D.C.: Center for Global Development.

CMH (Commission on Macroeconomics and Health). (2001) *Macroeconomics and health: Investing in health for economic development.* Report of the Commission on Macroeconomics and Health. Geneva: World Health Organisation.

Cohen, J. (2009) Drug approvals for neglected diseases increase along with more R&D funding. *Tufts Center for the Study of Drug Development Impact Report.* 11(6), 1-4.

Danzon P.M. (1998) The economics of parallel trade. *PharmacoEconomics*, 13(3), 293-304.

Danzon, P. and Towse, A. (2003) Differential pricing for pharmaceuticals: Reconciling access, R&D and patents. *Journal of Health Care Financing and Economics*. 3(3), 183-205.

Danzon, P., Mulcahy, A. and Towse, A. (2011) *Pharmaceutical prices in emerging markets*. NBER Working Paper. Cambridge, MA: National Bureau of Economic Research.

Dentzer, S. (2009) Eliminating neglected diseases in poor countries: A conversation with Andrew Witty. *Health Affair*s. 28(3), w411-w416.

DiMasi, J. and Grabowski, H.G. (2004) *Patents and R&D incentives: Comments on the Hubbard and Love trade framework for financing pharmaceutical R&D*. Submission to the World Health Organisation Commission on Intellectual Property Rights, Innovation and Public Health.

DiMasi, J.A., Hansen R.W. and Grabowski, H.G. (2003) The price of innovation: New estimates of drug development costs. *Journal of Health Economics.* 22(2), 151-185.

Dolgin, E. (2010) African networks launch to boost clinical trial capacity. *Nature Medicine.* 16(1), 8.

Farlow, A. et al. (2005) *Concerns regarding the Center for Global Development Report 'Making markets for vaccine'.* Geneva: Commission on Intellectual Property Rights, Innovation and Public Health.

Fink, C. (2001) Patent protection, transnational corporations, and market Structure: A simulation study of the Indian pharmaceutical industry. *Journal of Industry, Competition and Trade*. 1(1), 101-121.

Frew, S.E., Kettler, H.E., and Singer, P.A. (2008) The Indian and Chinese health biotechnology industries: Potential champions of global health? *Health Affairs.* 27(4), 1029-1041.

Frew, S.E., Liu V.Y. and Singer, P.A. (2009) A business plan to help the 'Global South' in its fight against neglected diseases. *Health Affairs.* 28(6), 1760.

Frick, K.D., Keuffel, E. and Bowman, R.J.C. (2001) Epidemiological, demographic, and economic analyses: Measurement of the value of trichiasis surgery in The Gambia. *Ophthalmic Epidemiology.* 8(2-3), 191-201.

GFHR (Global Forum of Health Research). (2002) *The 10/90 Report on Health Research 2001-2002*. Geneva: Global Forum for Health Research.

Gilead (Gilead Sciences, Inc.). (2011) *Expanding antiretroviral treatment coverage in the developing world*. Foster City, CA: Gilead Sciences, Inc. Available at http://www.gilead.com/pdf/GAPHistory.pdf [Accessed 27 May 2011].

Goodman, C. et al. (2009) Concentration and drug prices in the retail market for malaria treatment in rural Tanzania. *Health Economics*. 18(6), 727-742.

Goldstein, J. (2009) Where GSK is cutting sales reps, and where it's adding them. *Wall Street Journal Health Blog.* 28 October 2009.
Available at http://blogs.wsj.com/health/2009/10/28/where-gsk-is-cutting-sales-reps-and-where-its-adding-them/ [Accessed 27 May 2011].

Grabowski, H.G., Ridley D.B. and Moe, J.L. (2009) Encouraging Innovative Treatment for Neglected Diseases through Priority Review Vouchers. *In* Eggleston, K. ed. *Prescribing cultures and pharmaceutical policy in the Asia-Pacific*. Baltimore: The Brookings Institution. 347-366.

Gray, A. et al. (2006) *Donor investment choices: Modelling the value for money of investing in product development, public private partnerships as compared to other health care and non-health care interventions.* OHE Consulting Summary Report. London: Office of Health Economics.

Greenberg, H., Raymond, S.U. and Leeder, S.R. (2005) Cardiovascular disease and global health: Threat and opportunity. *Health Affairs*. Published online 25 January 2005. Available at http://content.healthaffairs.org/content/early/2005/01/25/hlthaff.w5.31/suppl/DC1 [Accessed 27 May 2011].

Hecht, R., Wilson, P. and Palriwala, A. (2009) Improving health R&D financing for developing countries: A menu of innovative policy options. *Health Affairs*. 28(4), 974-985.

Holmes, C.B. et al. (2010) Use of generic antiretroviral agents and cost savings in PEPFAR treatment programs. *Journal of the American Medical Association.* 304(3), 313-320.

Hsu, J.C. and Schwartz, E.S. (2008) A model of R&D valuation and the design of research incentives. *Insurance: Mathematics and Economics*. 43(3), 350-367.

Hubbard, T. and Love, J. (2004) A new trade framework for global health care R&D. *PLoS Biology* 2(2), e52.

HVMRT-WG (HIV Vaccines and Microbicides Resource Tracking Working Group). (2008) *Sustaining the HIV prevention research agenda: Funding for research and development of HIV vaccines, microbicides, and other new prevention options, 2000-2007.* [NP]: HIV Vaccines and Microbicides Resource Tracking Working Group.

IFPMA (International Federation of Pharmaceutical Manufacturers and Associations). (2010) *Developing World Health Partnerships Directory 2010.* Geneva: IFPMA.

Jack, A. (2008) GSK varies prices to raise sales. *Financial Times*. 16 March.

Jamison, D. et al. eds. (2006) *Disease control priorities in developing countries*. 2nd Edition. New York: Oxford University Press.

Jamison, D., Jha, P. and Bloom, D. (2009) *Copenhagen Consensus 2008 Challenge Paper: Disease Control*. Copenhagen: Copenhagen Consensus Center.

Kates, J. et al. (2010) *Donor funding for health in low- and middle-income countries*. Menlo Park: Kaiser Family Foundation.

Kesselheim, A.S. (2008) Drug development for neglected diseases -- The trouble with FDA review vouchers. *New England Journal of Medicine*. 359(19): 1981-1983.

Kettler, H. (2000) *Narrowing the gap between provision and the need for medicines in developing countries*. London: Office of Health Economics.

Kettler, H. and Collins C. (2002) *Using innovative action to meet global health needs through existing intellectual property regimes.* Study Paper 2b. London: Commission on Intellectual Property Rights.

Kettler, H. and Towse, A. (2002) *Public-private partnerships for research and development: Medicines and vaccines for diseases of poverty.* London: Office of Health Economics.

Kettler, H., White K. and Jordan, S. (2003) *Valuing industry contributions to public private partnerships for health development.* Geneva: Initiative on Public-Private Partnerships for Health.

Kremer, M. (2000) *Creating markets for new vaccines part II: Design issues*. NBER Working Paper. (7717). Cambridge, MA: National Bureau of Economic Research.

Kremer, M. (1998) Patent buyouts: A mechanism for encouraging innovation. *Quarterly Journal of Economics.* 113(4), 1137-1167.

Kremer, M. (2002) Pharmaceuticals and the developing world. *Journal of Economic Perspectives*. 16(4), 67-90.

Kremer, M. and Glennerster, R. (2004) *Strong medicine: Creating incentives for pharmaceutical research on neglected diseases*. Princeton: Princeton University Press.

Kremer, M., Towse, A., and Williams H. (2005) *Briefing note on advance purchase commitments*. London: UK Department for International Development Health Systems Resource Centre. Available at http://www.who.int/intellectualproperty/submissions/MichealKremerKTW_CIPIH_submit_2.pdf [Accessed 27 May 2011]

Kyle, M.K. and McGhan, A.M. (2009) *Investments in pharmaceuticals before and after TRIPS.* NBER Working Paper. (15468). Cambridge, MA: National Bureau of Economic Research.

Kyle, M.K. (2008) *Strategic responses to parallel trade.* NBER Working Paper. (12968). Cambridge, MA: National Bureau of Economic Research.

Kyle, M.K. and Ridley D.B. (2007) Would greater transparency and uniformity of health care prices benefit poor patients? *Health Affairs.* 26(5): 1384-1391

Lanjouw, J. (2006) A patent policy proposal for global diseases. *Innovations: Technology, Governance, Globalization.* 1(1), 108-114.

Lanjouw J. (1998) *Introduction of pharmaceutical product patents in India: Heartless exploitation of the poor and suffering?* NBER Working Paper. (6366). Cambridge, MA: National Bureau of Economic Research.

Laxminarayan, R. and Gelband, H. (2009) A global subsidy: Key To affordable drugs for malaria? *Health Affairs*. 28(4), 949-961.

Laxminarayan, R., Over M. and Smith, D.L. (2006) Will a global subsidy of new antimalarials delay the emergence of resistance and save lives? *Health Affairs.* 25(2), 325-36.

Laxminarayan, R. et al. (2010) Should new antimalarial drugs be subsidized? J*ournal of Health Economics.* 29(4), 445-456.

Levine, R. (2007) *A risky business: Saving money and improving global health through better demand forecasts*. Washington, D.C.: Center for Global Development.

Levine, R. et al. (2008) Demand forecasting for essential medical technologies. *American Journal of Law & Medicine.* 34: 225.

Levine, R., Kremer M. and Albright, A. (2005) *Making markets for vaccines.* The report of the Center for Global Development Advance Market Commitment Working Group. Washington, D.C.: Center for Global Development.

Lichtenberg, F. R. and Waldfogel, J. (2008) Does misery love company -- Evidence from pharmaceutical markets before and after the Orphan Drug Act. *Michigan Telecommunications and Technology Law Review*. 15(2): 335-357.

Loftus, P. (2010) Eli Lilly sets plans for emerging markets. *Wall Street Journal* [online]. 8 June.

Love, J. and Hubbard, T. (2007) The big idea: Prizes to stimulate R&D for new medicines. *Chicago-Kent Law Review*. 82(3), 1519-1548.

Matlin, S.A. et al. eds. (2008) *Health partnerships review: Focusing collaborative efforts on research and innovation for the health of the poor*. Geneva: Global Forum for Health Research.

Mehrpouya, A. et al. (2010) *Access to Medicine Index 2010*. Haarlem, NL: Access to Medicine Foundation. Available at http://www.accesstomedicineindex.org/sites/www.accesstomedicineindex.org/files/publication/Access_to_Medicine_Index_2010.pdf [Accessed 17 May 2011].

Moe, J., Grabowski, H.G. and Ridley, D. (2009) FDA Review Vouchers. *New England Journal of Medicine.* 360: 837-838.

Moran, M. (2005) A breakthrough in R&D for neglected diseases: New ways to get the drugs we need. *PLoS Medicine.* 2(9), e302.

Moran, M. et al. (2011) *Neglected disease research and development: Is the global financial crisis changing R&D?* Sydney: Policy Cures.

Moran, M. et al. (2009) *Neglected disease research & development: New times, new trends*. Sydney: Health Policy Division, the George Institute for International Health.

MSF (Médecins Sans Frontières). (2008) *Untangling the web of antiretroviral price reductions.* Geneva: Médecins Sans Frontières.

Novartis. (2011) *Novartis introduces GIAPA/TIPAP.* Novartis [online]. Available at http://www.corporatecitizenship.novartis.com/patients/access-medicines/access-in-practice/glivec.shtml [Accessed 31 May 2011].

Onwujekwe, O., Hanson K. and Fox-Rushby, H. (2004) Inequalities in purchase of mosquito nets and willingness to pay for insecticide-treated nets in Nigeria: Challenges for malaria control interventions. *Malaria Journal*. 3(1), 6-14.

Oxfam. (2007) Investing for life: Meeting poor people's needs for access to medicines through responsible business practices. *Oxfam Briefing Paper.* Oxford: Oxfam International.

Patouillard, E., Hanson K.G. and Goodman, C.S. (2010) Retail sector distribution chains for malaria treatment in the developing world: A review of the literature. *Malaria Journal*. 9(2), 50-64.

Pecoul, B.C.P., Trouiller. P. and Pinel, J. (1999) Access to essential drugs in poor countries: A lost battle? *Journal of the American Medical Association.* 281: 361-367.

PEPFAR (2010) *Report to Congress on costs of treatment in the President's Emergency Plan for AIDS Relief*. Washington, D.C.: President's Emergency Plan for AIDS Relief.

PF3. (2009) *Pharma Futures 3: Emerging opportunities.* London: SustainAbility Ltd.

Pogge, T. and Hollis. A. (2008) *The Health Impact Fund: Making new medicines accessible for all*. New Haven, CT: Incentives for Global Health.
Available at http://www.yale.edu/macmillan/igh/hif_book.pdf [Accessed 27 May 2011].

Reddy, K.S. (2004) Cardiovascular disease in non-Western countries. *New England Journal of Medicine*. 350(24), 2438-2440.

Riahi, F. (2002) Presentation at Pharmaceutical Innovation in the Global Economy. Wharton Impact Conference. Philadelphia: University of Pennsylvania. 4-5 October.

Ridley, D.B. and Calles Sánchez, A. (2010) Introduction of European priority review vouchers to encourage development of new medicines for neglected diseases. *Lancet.* 376(9774), 922-927.

Ridley, D.B., Grabowski, H.G. and Moe, J.L. (2006) Developing drugs for developing countries. *Health Affairs.* 25(2), 313-324.

Ridley, R.G. (2003) Product R&D for neglected diseases. Twenty-seven years of WHO/TDR experiences with public-private partnerships. *European Molecular Biology Organization reports*. 4(S1): S43-S46.

Rollings, M. (2007) Combating counterfeit drugs: An international problem. *Drug Topics.* 151(19), 30-32.

Rouse, D.J. ed. (2001) *Economics of TB drug development: New data for new research*. New York: The Global Alliance for TB Drug Development.

Sabot, O.J. et al. (2009) Piloting the global subsidy: The impact of subsidized artemisinin-based combination therapies distributed through private drug shops in rural Tanzania. *PLoS ONE* 4(9), e6857.

Sehgal, S. (2002) *Private equity investments in pharmaceuticals: An Asian LDC perspective.* Paper presented at Pharmaceutical Innovation in the Global Economy. Wharton Impact Conference. Philadelphia: University of Pennsylvania. 4-5 October.

Seiter, A. (2008) *IPRs and access to "new essential drugs*. World Bank [online]. Available at http://siteresources.worldbank.org/INTHSD/Resources/Presentations/454393-1249391374015/IPRsandAccesstoNewEssentialDrugsJune2008.pdf [Accessed 31 May 2011].

Shah, R. (2002) *Accelerating the introduction of new vaccines into developing countries*. Paper presented at Pharmaceutical Innovation in the Global Economy. Wharton Impact Conference. Philadelphia: University of Pennsylvania. 4-5 October.

Towse, A. and Kettler, H. (2005a) *A Review of IP and non-IP incentives for R&D for diseases of poverty. What type of innovation is required and how can we incentivise the private sector to deliver it?* Working Paper for the Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH). Geneva: World Health Organization.

Towse, A. and Kettler, H. (2005b) Advance price or purchase commitments to create markets for treatments for diseases of poverty: Lessons from three policies. *Bulletin of the World Health Organization. 83(4), 301-307. Organization*. 83(4), 301-307.

Troullliller, P. et al. (2002) Drug development for neglected diseases: A deficient market and a public-health policy failure. *Lancet.* 359(9339), 2188-2194.

UNITAID. (2010) *UNITAID statement on the medicines patent pool*.
Available at http://www.accesstomedicineindex.org/content/unitaid-statement-medicines-patent-pool [Accessed 27 May 2011].

Vaitheeswaran, V.V. (2010) *Open labs, open minds: Breaking down the barriers to innovation and access to medicines in the developing world.* Interview with Andrew Witty for the Council Foreign Relations. 20 January. Available at http://www.cfr.org/poverty/open-labs-open-minds-breaking-down-barriers-innovation-access-medicines-developing-world/p21273 [Accessed 31 May 2011].

Vilela, C. (2002) *Private equity venture capital market: Ingredients for success*. Paper presented at Pharmaceutical Innovation in the Global Economy. Wharton Impact Conference. Philadelphia: University of Pennsylvania. 4-5 October.

Wagstaff, A. et al. (2009) Extending health insurance to the rural population: An impact evaluation of China's new cooperative medical scheme. *Journal of Health Economics*. 28(1), 1-19.

Watal, J. (2000) Pharmaceutical patents, prices and welfare losses: Policy options for India under the WTO TRIPS agreement. *World Economy.* 23(5), 733-752.

Weiner, D. (2002) *HIV-1, high technology DNA vaccines and the developing world: A match?* Paper presented at Pharmaceutical Innovation in the Global Economy. Wharton Impact Conference. Philadelphia: University of Pennsylvania. 4-5 October.

WHO-IMPACT. (2006) *Counterfeit medicines: An update on estimates*. Geneva: World Health Organization IMPACT (International Medical Products Ant-Counterfeiting Taskforce).

WHO (World Health Organisation). (2006) *Public health, innovation and intellectual property rights*. Report of the Commission on Intellectual Property Rights, Innovation and Public Health. Geneva: World Health Organisation.

WHO (World Health Organisation). (2008) *Global strategy and plan of action on public health, innovation and intellectual property*. Agenda Item 11.6. Sixty-First World Health Assembly. 24 May.

WHO (World Health Organisation). (2010) Research and development -- coordination and financing. Report of the World Health Organization Expert Working Group on Research and Development Financing. Geneva: World Health Organization.
Available at www.who.int/phi/documents/ewg_report [Accessed 27 May 2011].

Wilson, P. and Palriwala, A. (2010) *Consultation draft -- Prizes for global health technologies: An assessment with a case study on TB diagnostics.* Washington, D.C.: Results for Development Institute .

Yach, D., Struckler, D. and Brownell, K.D. (2006) Epidemiologic and economic consequences of the global epidemics of obesity and diabetes. *Nature Medicine.* 12(1), 62-66.

Yadav, P. (2010) *Differential pricing for pharmaceuticals: Review of current knowledge, new findings and ideas for action.* A study conducted for UK Department for International Development. Zaragoza, Spain: MIT-Zaragoza International Logistics Program.

Yadav, P., Curtis, K. and Sekhri, N. (2007) *Mapping and realigning incentives in the global health supply chain*. Washington, D.C.: Center for Global Development.

Yin, W. (2008) Market incentives and pharmaceutical innovation. *Journal of Health Economics*. 27(4), 1060-1077.

Zeckhauser, R. (2002) *Health externalities from LDC pharmaceutical use*. Paper presented at Pharmaceutical Innovation in the Global Economy. Wharton Impact Conference. Philadelphia: University of Pennsylvania. 4-5 October.

Zhou, B. et al. (2008) Social health insurance and drug spending among cancer inpatients in China. *Health Affairs.* 27(4), 1020-1027.