Civil Society Report on Intellectual Property, Innovation and Health

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Action Research and Community Health, India
Alternate Solutions Institute, Pakistan
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Instituto Libre Empresa, Peru
Instituto Libertad y Progreso, Colombia
International Policy Network, United Kingdom
Jerusalem Institute for Market Studies, Israel
Liberty Institute, India
PHD Chamber of Commerce, India

Contents

Introduction

This report is a response from a global coalition of concerned civil society groups to the World Health Organization's Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH).

The CIPIH was instituted at the World Health Assembly in 2003, with the aim of collecting data and proposals from interested actors to produce an analysis of the issues surrounding intellectual property, innovation and public health, with a particular view of recommending the best ways to incentivise research and development for the diseases of poverty. The Commission hopes to present its recommendations to the World Health Assembly in 2006.

The remit of the CIPIH was to:

- Summarise the existing evidence on the prevalence of diseases of public health importance with an emphasis on those that particularly affect poor people and their social and economic impact;
- Review the volume and distribution of existing research, development and innovation efforts directed at these diseases;
- Consider the importance and effectiveness of intellectual property regimes and other incentive and funding mechanisms in stimulating research and the creation of new medicines and other products against these diseases;
- Analyse proposals for improvements to the current incentive and funding regimes, including intellectual property rights, designed to stimulate the creation of new medicines and other products, and facilitate access to them;
- Produce concrete proposals for action by national and international stakeholders.[1]

As such, the CIPIH should represent an important and influential contribution to the ongoing debate over innovation and public health.

Our report

The task of producing an analysis of intellectual property rights, innovation, and public health is formidable. Inevitably, the CIPIH's efforts to balance different and sometimes conflicting political agendas, of the kind that invariably arise in intergovernmental fora, raises the prospect that its Report will be a political compromise rather than an independent assessment of the available evidence.

Contributors to this study are particularly concerned that for political reasons the CIPIH may avoid discussion of important issues, such as the effectiveness of institutions and governance structures in many countries, which affect both access to medicines and the incentives to develop new medicines. Moreover, we were concerned that the CIPIH report may take a less than impartial view of the role of government intervention in the innovation system.

The contributors therefore set out to produce an independent report, following the same remit as the CIPIH. Our report is the result of a collaborative effort between researchers from around the world and is intended to provide a more consistent, more independent and more substantive contribution to the debate on these issues.

About the sponsoring organisations

This report is the product of close collaboration between a number of independent, non-partisan civil society organisations, including:

- Action Research and Community Health, India
- Alternate Solutions Institute, Pakistan
- ESEADE University, Argentina
- Free Market Foundation, South Africa
- Fundación Atlas 1853, Argentina
- Global Bioscience Development Institute, USA
- Imani, the Centre for Humane Education, Ghana
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- Instituto Libertad y Progreso, Colombia
- International Policy Network, United Kingdom
- Jerusalem Institute for Market Studies, Israel
- Liberty Institute, India
- PHD Chamber of Commerce, India

The report was conceptualised jointly by these organisations and representatives of each had a hand in drafting and editing the document. While several of the organisations receive financial support from parties that have an interest in the issue of drug development, including both research-based and generic pharmaceutical companies, this report was funded entirely from general contributions. In addition, in order to ensure the report's independence, financial supporters had no input or oversight of any kind regarding the report's structure, contents or conclusions.

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Executive summary

The prevalence of the diseases of poverty

- Around 45 percent of the disease burden in lower income countries is caused by poverty-related diseases. These diseases are strongly correlated with poor nutrition, indoor air pollution and a lack of access to proper sanitation and health education.
- A large proportion of these diseases could be prevented with existing treatments and techniques. Unfortunately, access to essential medicines remains extremely low in many areas of the world. According to the WHO, an estimated one-third of the world population lacks regular access to essential drugs, with this figure rising to over 50 percent in the poorest parts of Africa and Asia. It has been estimated that around 3 million children die every year because they do not receive basic medicines and treatments.

Research and development for the diseases of poverty

- The nature and spread of diseases suffered in both rich and poor countries is converging rapidly. In absolute terms, non-communicable diseases now kill greater numbers of people in the lower-income countries than they do in high-income countries, with four out of five deaths from chronic diseases now occurring in the former. Cardiovascular diseases are now among the most significant killers in lower-income countries. It is important that current and future R&D for these diseases is encouraged. This notwithstanding, the global pattern of R&D reflects the global burden of disease to a greater extent than is often claimed.
- Research and development activity around the diseases of poverty is currently taking place at an unprecedented level, largely as a result of the creation of Public Private Partnerships. This R&D activity is expected to increase over the next few years as these PPPs become more established.
- Most important advances in pharmacology were originally made with wealthy markets in mind. These range from such things as vaccines for childhood diseases to ARV drugs. Lower-income countries have benefited enormously from this technology transfer and will continue to do so in the future – providing the costs of trade are lowered and governments of lower-income countries properly address their failures of governance which hinder the distribution of medicines.

Barriers to access

- Lower income countries have often not benefited from the full potential of modern drugs because of a number of self-generated policy failures that actively impede access to medicines. These include:
  - Excessive tariffs and taxes on both imported and domestically produced drugs, which can inflate the cost of medicines by up to one-third. While these artificial price inflators raise little money for government treasuries, they are regressive taxes that price the poor and sick out of treatment.
  - Weak healthcare systems that hinder the effective distribution of drugs. While this obviously includes such things as effective hospitals and nurses, it also extends to the wider infrastructural constraints on the delivery of

drugs such as poor roads and unreliable electricity networks. Research shows that extra funding of public health services in lower-income countries rarely translates into improved services for the poor.
  - Lack of health insurance. Governments in lower-income countries also fail to provide the necessary institutional environment for functional risk pooling mechanisms (or health insurance) that would widen access to medicines by removing the need to make out of pocket payments for healthcare.
  - The intervention of international public health authorities, such as the WHO, is no guarantee that medicines will be widely distributed. Both its '3 by 5' and Roll Back Malaria programmes have failed to achieve their self-imposed targets, and may have made matters worse by increasing drug resistance.
- It is unlikely that good health will ever be sustained without long-term wealth creation that can pay for the ongoing improvements in water, sanitation, nutrition, living conditions, health education and hospitals which are vital for the control of diseases such as malaria, tuberculosis and AIDS.
- Meanwhile, economic growth is most likely to occur on a sustainable basis when societies have economic freedom (secure property rights, freedom to use them, freedom of contract and the rule of law).
- Unfortunately, the governments of poor countries continue to hinder the creation of wealth, imposing obstacles in the way of owning and transferring property, imposing unnecessary regulatory barriers on entrepreneurs and businesses, and restricting trade through extortionate tariffs.
- All the above factors have a detrimental knock-on effect for pharmaceutical innovation, because they shrink the demand for medicines. Commercial drug developers are unlikely to invest large amounts of capital into a new drug if it is never likely to penetrate properly its intended market.

Barriers to innovation

- Weak intellectual property legislation in countries with incipient or extant knowledge-based industries acts as a serious disincentive on R&D into the diseases of poverty, not least because it jeopardises the ability to generate enough sales to cover the extremely high costs of innovation.

  This is particularly true of highly politicised diseases such as HIV/AIDS; with countries such as Brazil threatening to implement compulsory licenses for ARVs, it becomes more difficult for R&D companies to invest resources in the search for new medicines.

  Strong intellectual property legislation can also go some way to encouraging the development of an indigenous R&D industry in countries where it currently does not exist. As India comes to terms with its recently enacted patent legislation, for example, more companies are turning to value-added R&D work, rather than merely producing copies. It is likely these companies are also finding commercial benefit in developing drugs for diseases prevalent among local populations, which, due to their lower cost base, can be developed at prices far lower than equivalent development in wealthy countries.
- There are a number of other elements in the public policy mix which actively reduce incentives for commercial R&D into diseases that mainly afflict lower income countries. These include:
  - Burdensome pre-market regulations which drive up the cost of development. Research suggests that increasing regulatory requirements are directly responsible for the declining number of New Chemical Entities each year. Many lower-income countries, for example South Africa, require new drugs to undergo their own approval process, even if those drugs have already been approved in the US, EU and Japan. This can add two or more years to the time it takes to bring a drug to market. Many of these regulatory steps are unnecessarily precautionary and add both time and cost to drug development.
  - Price controls, which serve to discourage companies from serving markets where they are in place. They can also encourage illegal counterfeit medicines. They also have a negative

impact on the distribution of medicines, by squeezing the margins of local pharmacies. In many lower-income countries, pharmacies are often the only healthcare many people receive, so the effects of price controls on the poorest populations could be disastrous. Price controls also discourage innovation by eroding the profitability of drugs, which then leaves fewer resources to dedicate to R&D.

– An inability to enact and enforce price differentiation strategies, which prevents companies from selling their products at different prices within poorer countries. Price differentiation is undermined by price controls, the threat of compulsory licenses, and weak rule of law.

Current R&D proposals scrutinised

- Notwithstanding these barriers to access and innovation, there is a need for new medicines to be developed for the diseases of poverty, not least because of increasing drug resistance. However, many of the proposals on the table to create incentives for R&D into such new drugs, while not without their merits, also suffer from significant flaws.
- One such suggestion is to increase direct, public funding for private or public entities engaged in such R&D. However, the evidence suggests that such spending is wasteful, inefficient, hostage to vested-interests, and unlikely to produce beneficial results.
- Transferable patent extensions may work but need to be given careful consideration. A scheme that allowed a drug company to extend the patent on a single blockbuster for a year or more, for example, would effectively force the users of that drug to pay for the development of a drug for a completely different disease. This is ethically dubious and would likely be met with fierce resistance by patient groups. If, however, the patent extension was spread more thinly, for example by granting a short patent extension to many drugs, then these concerns would likely be alleviated.
- Advance Purchase Commitments have been accepted by the G8 as an appropriate mechanism for generating a malaria vaccine. However, it is far from clear that such schemes are either efficient or workable. Because the value of the end product must be determined by a committee rather than by market processes, it is likely that the cost of the final product will be inflated. Furthermore, because they are a 'winner takes all' prize, APCs will stifle incremental, follow-on competition, meaning that few improvements will be made to the final product. This will have significant implications in case of resistance or special clinical requirements for subpopulations. Finally, the historical record of prizes – of which APCs are one particular example – is far from encouraging.
- Orphan drug legislation has been moderately successful in encouraging drug companies to develop drugs for 'orphan' diseases in the US, largely by providing a favourable tax and fast-track regulatory environment. This could feasibly be replicated for R&D into the diseases of poverty.
- The success of open source in software development has led some to argue that it could be replicated in drug development. While this may be a workable model for the early stages of development, open source is unlikely to provide the large amounts of capital and labour required to take a drug through extensive clinical trials.
- Proposals that seek to restrict the granting of patents for so-called 'me-too' drugs misunderstand the incremental nature of innovation. The vast majority of drugs that exist today are incremental improvements on preceding drugs. The existence of many similar drugs in the same class is vital for improving safety, efficacy, selectivity and utility of drugs within a specific class.
- Public Private Partnerships (PPPs) are proving to be an effective way of directing R&D towards the diseases of poverty. PPPs are largely responsible for the current, unprecedented levels of research and development activity around the diseases of poverty. At the end of 2004, over 60 neglected disease drug development projects were in progress, the highest level to date. Furthermore, research shows that these partnerships are conducting their work more quickly

and at a comparatively lower cost than industry standards, while the costs are being largely borne by the private sector.

- There is some concern from researchers that introducing policies designed to 'kick start' innovation from scratch will undermine the excellent progress being made by PPPs. If companies are presented with pseudo-market mechanisms such as APCs, for example, there is a risk they will divert resources away from the successful, effective and less costly PPP ventures towards these more risky projects.

Recommendations

- Policymakers in poor countries must, as a priority, remove barriers to the provision of healthcare, especially taxes, tariffs and regulatory barriers that currently prevent the poor from obtaining essential medicines.
- Policymakers in poor countries should also improve the institutional environment more generally, so that people are able to generate wealth and thereby ensure that healthcare systems become self-sustaining – and provide a strong demand driver for the development of new drugs.
- Policymakers in higher-income countries should provide a regulatory and tax environment that nurtures PPPs as well as pure private sector development of drugs for the diseases of poverty.
- Countries with slow and inefficient patent offices should introduce measures to improve the speed and efficiency of the patenting process. This might entail the introduction of incentive-based pay schemes, the contracting out of services to the private sector, or the merging of patent offices in different countries.
- All countries should consider improving the efficiency and effectiveness of their drug regulatory agencies, so that companies developing new drugs are subject to fewer and less arbitrary restrictions on the marketing of their products, while safeguarding consumers.
- Governments should avoid creating a new intergovernmental body for the promotion of drug development, since such a body is unlikely to be an efficient or effective vehicle for increasing drug research and development.

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1

The burden of disease, causes, impact and cures

This chapter considers the severity of the disease burden affecting poorer countries and puts it into context. The chapter begins with a description of the distribution of the diseases of poverty. It then provides an account of the impact of these diseases, and ends with an assessment of the prospects for reducing the burden of disease.

The burden of disease

Table 1 shows the World Health Organisations estimates of the proportion of deaths from poverty-related diseases (defined as diseases that primarily affect the poor) in poor and rich countries. While not without its problems, this WHO measure at least gives us a ball-park estimate of the global burden of disease and its distribution. According to this measure, the diseases of poverty account for 45 percent of the disease burden in the poorest countries compared with only 6 percent in rich countries (WHO, 2002a).

The diseases of poverty are strongly correlated to poor nutrition, indoor air pollution and a lack of access to proper sanitation and health education. Diarrhoeal diseases are a particularly pernicious problem for children in the poorest countries, with morbidity rates currently increasing (Guerrant et al., 2002).

The economic impact of disease

The health of a country's population affects its rate of economic growth (Barro, 1991; Bloom & Williamson, 1998; Wagstaff, 2002). Good nutrition, for example, allows working adults to be more productive and thus spend more time generating income. Good nutrition among children is also important for promoting long-term economic growth, because it improves their cognitive and physical ability as adults. This helps to ensure that the future adult population is economically productive (Fogel, 2004).

Table 1 **Deaths caused by poverty-related diseases**

% of deaths caused by/in	*High mortality low-income countries*	*Low mortality low-income countries*	*High-income countries*
Infectious and parasitic diseases	34.1	24.8	2.1
Respiratory infections	9.9	8.0	3.7
Perinatal and maternal conditions	8.4	6.8	0.4
Nutritional deficiencies	1.3	1.1	0.0
Tropical diseases	0.5	0.3	0.0
Total 'poverty-related' diseases	54.1	40.7	6.2

Source: WHO (2002a)

Healthier people who live longer also have stronger incentives to invest capital in developing their skills, because they expect to accrue the benefits over longer periods. If a child is more likely to reach adulthood, the parents are more likely to risk scarce resources on its education, for example – an investment that can lead to higher productivity and income in adulthood. Improved child health can also reduce the economic burden on both families and governments, freeing up resources for investment elsewhere (Karoly et al., 1998).

Just as good health may facilitate economic growth, poor health can constrain it. This is particularly true of the poorest countries of the world, which typically have the greatest disease burdens. It is worth examining the dampening effect poor health can have on development.

Poor health reduces economic development in part by reducing the number, availability and abilities of workers. If the population remains unhealthy for a sustained period, this can reduce the rate of economic growth (Over, 1991). In turn, this reduces the amount of resources the government and individuals are able to spend on education, health, and living conditions, which may further exacerbate the cycle of poor health and poverty.

The most prevalent infectious diseases of poverty — respiratory infections, HIV/AIDS, diarrhoeal diseases, tuberculosis, and malaria — certainly have a large and negative impact on productivity. The economic impact of HIV/AIDS is particularly worrisome, because more than 80 percent of global mortality from the disease occurs among those of working age. The disease's impact on the labour force is heightened by the fact that its political significance results in a massive diversion of resources away from fighting other diseases of poverty (Craven et al., 2005), which in turn exacerbates their economic consequences. This is especially true of those diseases prevalent in children, particularly acute lower respiratory infections (ALRI) and diarrhoeal diseases, both of which are likely to harm children's cognitive abilities in subsequent years.

Diarrhoeal diseases

Diarrhoeal diseases can have a particularly damaging impact on productivity. Of all childhood infectious diseases, these seem to have the greatest effect on human development. They reduce appetite, alter feeding patterns, and decrease absorption of nutrients, thereby slowing the rate at which children grow and inhibiting brain development. The number of diarrhoeal episodes in the first two years of life has been shown not only to affect growth but also fitness, cognitive function, and school performance (Guerrant et al., 2002). As affected children become adults and enter the labour force, their poor stamina and impaired intellect reduce their productivity.

A recent study showed that diarrhoeal diseases form the bulk of the related health risk from poor sanitation (Prüss et al. 2002). A total of some 4 billion cases per year are estimated to result in between 1 and 2 million deaths and the loss of between 37 and 76 million disability adjusted life years (DALYs), with 90 percent of deaths occurring among children under 5. The study's authors added impacts of other water-associated diseases (e.g. schistosomiasis, trachoma and intestinal helminth infections), and then concluded that illness caused by poor water, sanitation and hygiene result in an additional 2 million deaths and 82 million lost DALYs per year. One study estimates the annual economic costs associated with poor access to water and sanitation are around US $40 billion (Rijsberman, 2004).

Malaria

Malaria creates an economic burden not only through direct costs on households — which must spend money on preventative and curative measures such as insecticide-treated bednets and anti-malarial drugs — but also through indirect costs such as lost work time through illness or tending to sick relatives (Chima, Goodman & Mills, 2003). The impact of malaria on a country's economic development may be substantial. Gallup and Sachs (2000) estimate that countries with a relatively higher prevalence of malaria grew 1.3 percent per year less between 1965 and 1990 (controlling for other influences on economic growth), and that a 10 percent reduction in malaria is potentially associated with 0.3 percent higher annual economic growth.

Controlling malaria, then, can be good for a nation's economic development as well as its health. In Mymensingh (now in Bangladesh), for example, crop yields increased 15 percent when malaria was eradicated in the 1960s, because farmers could spend more time and effort on cultivation (Easterlin, 1996). In other regions, the elimination of seasonal malaria enabled farmers to plant a second crop for the first time in their history. The near-eradication of malaria in Sri Lanka between 1947 and 1977 raised its national income by an estimated 9 percent (World Bank, 1993).

Malnutrition

Malnutrition, one of the most obvious symptoms of poverty, also reduces economic growth through its negative effect on productivity. Research has demonstrated a link between protein-energy malnutrition, and iron and iodine deficiency, and lower productivity in adults. Children born to malnourished mothers or who are malnourished during childhood can suffer cognitive losses that are associated with lower productivity in adulthood. According to the World Bank, malnutrition stunts the intellectual and physical development of more than 100 million children worldwide (World Bank, 2006). Malnourished children also place additional burdens on health and education systems because they have greater needs for healthcare and are more likely to require more intensive teaching at school (Horton, 1999).

Chronic diseases

Chronic diseases also pose significant economic costs for both lower and higher income countries. Cardiovascular disease, for example, requires costly and prolonged clinical care, thereby entailing costs for both health systems and individuals. Cardiovascular diseases frequently affect individuals who are otherwise in their economic prime, thereby disadvantaging both dependent families and the broader economy. This is especially relevant in lower-income countries such as India, whose rapidly burgeoning and economically productive middle-classes suffer from a relatively high incidence of such diseases.

The impact of economic growth on the burden of disease

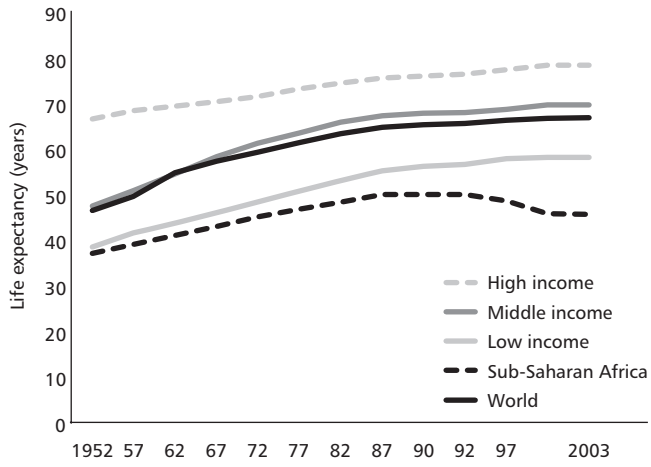
While disease clearly has a negative impact on economic development, there is also considerable evidence that economic development reduces the burden of disease. In a seminal 1996 study, economists Lant Pritchett and Lawrence Summers showed that increases in income can lead to dramatic improvements in health. By conducting a series of cross-country regressions, they found a strong causative effect of income on infant mortality, and demonstrated that if the developing world's growth rate had been 1.5 percentage points higher in the 1980s, half a million infant deaths would have been averted.

In fact, the health of the world's population has been improving since modern economic growth began in the early 19th Century. Infant mortality and life expectancy rates have both improved dramatically, and food is more abundant and more affordable. These indicators have improved due to an increased understanding of the causes of ill health – such as poor sanitation – as well as the development of technologies such as vaccines and antibiotics (Goklany, 2001). During the second half of the 20th Century the diffusion of this technology and knowledge to lower-income countries increased access to more sanitary living conditions and new medicines. Without increases in wealth, it would not have been possible to make better sanitation and clean water more widely available, or to purchase life-saving medical technologies or pay the personnel required to administer them. In large part as a result of these increases in wealth, the 20th Century saw rapid increases in life expectancy worldwide (Figure 1).

Wealthier, then, is clearly healthier, and historically, increases in wealth have tended to precede improvements in health. The clear conclusion is that an important part of any strategy to reduce the burden of disease must include improving the conditions that enable wealth to be created.

It is unlikely that good health will ever be sustained without long-term wealth creation that can pay for the ongoing improvements in water, sanitation, nutrition, living conditions, health education and hospitals which

Figure 1 **Economic growth and rising life expectancy**



Source: World Bank, 2005

are vital for the control of diseases such as malaria, tuberculosis and AIDS.

Unfortunately, the governments of poor countries continue to hinder the creation of wealth, imposing obstacles in the way of owning and transferring property, imposing unnecessary regulatory barriers on entrepreneurs and businesses, and restricting trade through extortionate tariffs. If these issues were addressed in those countries, many diseases of poverty would be relegated to history, as they have been in the world's wealthiest countries.

Treatments for the diseases of poverty

While economic growth is clearly part of the solution in the medium to long term, many of those who die from the diseases of poverty could be saved if appropriate action were taken more immediately. An authoritative study published in 2003 estimated that over 10 million children die prematurely (and thus unnecessarily) each year, almost all in low- or middle-income countries (Black et al., 2003). Most of these deaths are caused by a small number of preventable diseases, such as diarrhoea, measles, malaria and causes related to malnutrition.

Only one-half (approximately) of sub-Saharan African children are vaccinated against childhood diseases, and in isolated areas that number is as low as one child in 20 (WHO, 2002b). It is estimated that over 80 percent of child diarrhoeas, child malaria and other childhood illness such as measles and tetanus could be prevented using existing treatments (Jones & Stetekee, 2004). In other words, at least three million child lives could be saved each year if these existing medicines could be distributed effectively to all those who would benefit from them. As observed in the World Health Organization's 2002–2003 Medicines Strategy Report:

> "An estimated one-third of the world population lacks regular access to essential drugs, with this figure rising to over 50 percent in the poorest parts of Africa and Asia. And even if drugs are available, weak drug regulation may mean that they are substandard or counterfeit."

Diseases the incidence and/or impact of which could be dramatically reduced using existing techniques include:

- Tuberculosis, malaria and HIV/AIDS, which account for nearly 18 percent of the disease burden in the poorest countries (WHO, 2004).
- Respiratory infections caused by burning biomass fuels and low-grade coal in poorly ventilated areas also constitute a significant health burden for poor people. According to the WHO, exposure to biomass smoke increases the risk of acute lower respiratory infections (ALRI) in childhood, particularly pneumonia. Globally, ALRI represent the single most important cause of death in children under 5 years and account for at least two million deaths annually in this age group (Bruce et al., 2002).
- Diarrhoeal diseases, caused by the poor sanitation which is endemic in economically deprived areas, may be easily and cheaply treated through oral re-hydration therapy. However, diarrhoeal diseases still claim 1.8 million lives each year, (WHO, 1999) and are the second biggest killer of children worldwide, after respiratory infections.
- Malaria can be prevented through a combination of indoor residual spraying of dwellings with insecticides, the use of insecticide treated bed nets

and the use of prophylactic medicines. Malaria infections can be cured with drugs such as quinine, mefloquine or artemisinin combination therapy (Muheki et al., 2004; PAHO, 2006).

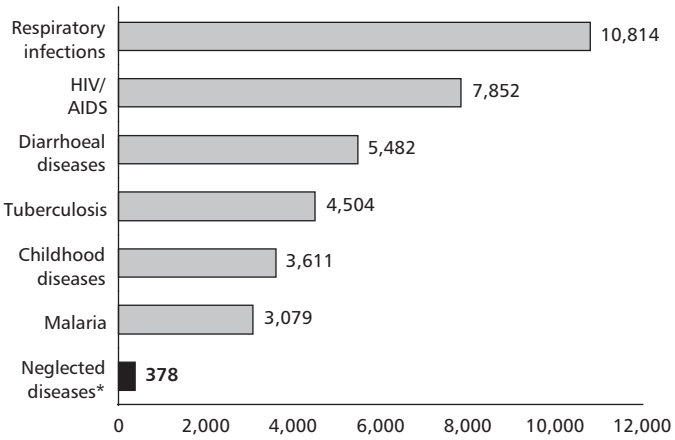
- Yellow fever — a vector-borne, viral disease with high mortality rates — can be prevented by using prophylactic vaccination. An affordable and effective vaccine is available, but nearly all countries in which the disease is enzootic prefer to wait until an epidemic is evident before mass-treatment of the affected population is undertaken (Nasidi, Monath et al. 1993; Monath 2005). Education can also play an important role in reducing the incidence of insect-borne diseases, for example by encouraging people to remove sources of stagnant water (insect breeding sites) from near their dwellings.
- Tuberculosis can be prevented by improving nutrition, and can be treated with DOTS therapy. This method can detect and cure disease in up to 95 percent of infectious patients, even in the poorest countries (WHO, 1999).
- Education is vital for the prevention of HIV/AIDS – and this entails the full engagement of civil society. A combination of anti-retrovirals (ARVs) and good nutrition can help to control the viral load and suppress the symptoms of HIV/AIDS.
- Treatable childhood diseases such as polio, measles and pertussis, account for only 0.2 percent of Disability Adjusted Life Years (DALYs) in high-income countries, while they account for 5.2 percent of DALYs in high mortality lower income countries (WHO, 2002a). Vaccines for these diseases have existed for at least 50 years, yet only 53 percent of children in sub-Saharan Africa were immunised with the diphtheria-tetanus pertussis (DTP) jab in 2000 (WHO, 2002b).
- Malnutrition particularly affects people in poor countries. In particular, micronutrient deficiencies contribute to illness and poor health. For example, as a result of Vitamin A deficiency, 500,000 children become blind each year (WHO, 1995) and many of them die, despite the fact that such outcomes can be avoided by inexpensive, easy-to-administer food supplements (WHO, 1997). Vitamin A deficiency also weakens the immune system, leaving children vulnerable to other illnesses such as diarrhoea and measles. Estimates suggest that Vitamin A deficiency contributes to or causes approximately 800,000 childhood deaths each year (WHO, 2002a).
- Dengue is a mosquito-borne viral infection prevalent in over 100 countries. According to the WHO, two-fifths of the world's population is at risk from dengue, and there are around 50 million infections every year.[2] Dengue can be prevented with a range of techniques to control insects. These include covering water containers and applying insecticides to larval habitats. During the 1950s the principal vector, *Aedes aegypti*, was eradicated from 22 countries in the Americas by the application of DDT.
- Pertussis (whooping cough) is a particular threat to infants. Somewhere in the range of 20 to 40 million cases occur every year, mostly in less developed countries, and as a result, between 200,000 and 400,000 die every year.[3] An effective vaccine against pertussis has existed for some years, but currently 20 percent of children worldwide do not receive it.
- Leprosy was for many centuries an incurable and widespread disease. However, the development and adoption, in the early 1980s, of multidrug therapy (dapsone, rifampicin and clofazimine) has led to a 90 percent decline in its prevalence.[4]

Re-assessing the '10/90' gap

There remain diseases which affect millions of poor people for which there are currently no effective treatments. While deaths from such diseases are clearly tragic, much confusion has been created as a result of a spurious claim that these 'neglected' diseases constitute the most urgent health problems in lower-income countries. The diseases defined by the WHO as 'neglected' – African trypanosomiasis, Chagas disease, and leishmaniasis – account for a relatively small proportion of the disease burden in poor countries (Figure 2). According to the WHO's 2004 World Health Report, such diseases accounted for only 0.5 percent of deaths in high mortality poor countries, and only 0.3 percent of deaths in low mortality poor countries (WHO, 2004).

The exaggeration of the 'neglected disease' problem has become formalised through the creation of a construct

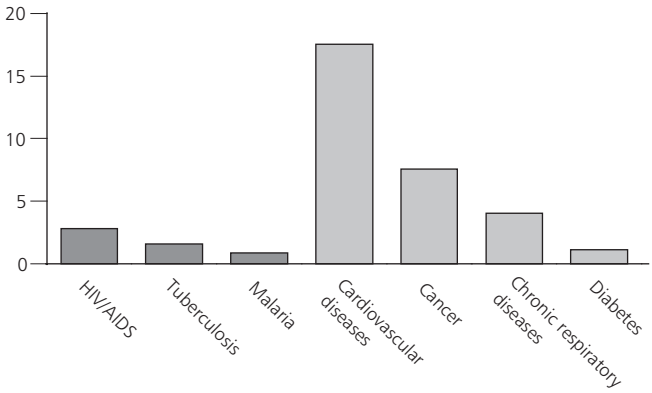
Figure 2 **Number of daily deaths from diseases**



*Neglected diseases are defined as African trypanosomiasis, Chagas disease and leishmaniasis

Source: WHO (2003b)

Figure 3 **Projected global deaths by cause**
2005 (all ages), millions

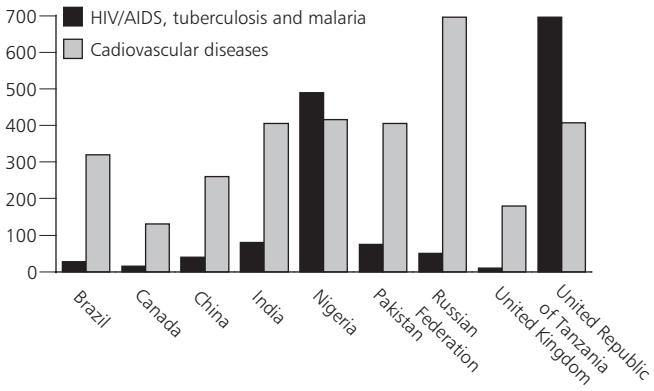


Source: WHO (2005a)

known as the '10/90 gap', the premise of which is that 90 percent of resources devoted to health research are spent on diseases that affect only 10 percent of the world's population. Again, this is factually incorrect (Figures 2, 3, 4 and 5).

The nature and spread of diseases suffered in both rich and poor countries is converging rapidly. According to the WHO, ailments such as cardiovascular disease, cancer and diabetes now account for 45 percent of the global disease burden. Around 80 percent of this burden now occurs in low and middle-income countries (WHO, 2005a). Chronic diseases cause four out of five deaths in lower-income countries. In absolute terms, more people in the lower-income countries (compared to higher-income countries) die as a result of non-communicable diseases. Cardiovascular diseases are one of the most significant causes of death in lower-income countries (Figures 3 and 4).

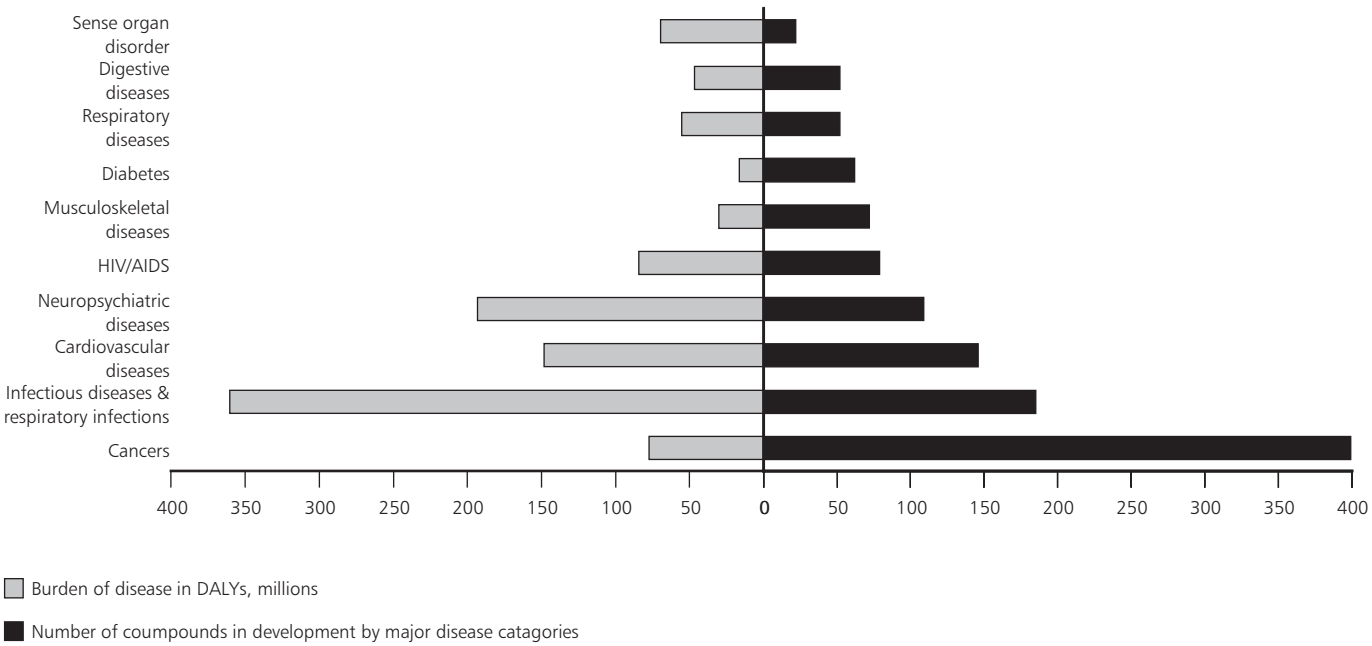
Figure 4 **Projected death rates by specific causes for selected countries**
2005 (all ages)



Source: WHO (2005a)

The WHO argues that much of this disease burden is attributable to less healthy diets and increasing physical inactivity. This may be so, yet the global rise of chronic diseases is also partly the result of more people living beyond middle age, thanks to greater global economic growth and prosperity. The prevalence of chronic disease, however, does challenge the myth that the current commercial R&D paradigm is failing to produce drugs that meet the needs of the global disease burden. Significant resources currently are being deployed towards developing treatments for cancers, cardiovascular diseases, neuropsychiatric diseases and diabetes. In fact, levels of drug development increasingly reflect the global disease burden, so lower-income countries therefore stand to benefit from drugs that are currently in the R&D pipeline (Figures 5 and 6).

Figure 5 **The global disease burden vs. number of compounds in development**



Sources: PhRMA (2005) and WHO (2004)

Lower-income countries also currently benefit from drugs that were originally developed for wealthier markets. Polio, pertussis (whooping cough) and diphtheria, for example, were once endemic in wealthier countries, but have been practically eradicated from these areas due to simple vaccines that were developed a few decades ago.

Now, three-quarters of the world's children — including millions in low-income countries — are vaccinated against such diseases, saving at least three million lives a year and preventing long term illness and disability in millions more. Tuberculosis treatments were originally devised to combat the disease in wealthier countries, and many populations in lower-income countries now reap the dividends of this advance in medical science in the form of mass vaccination programmes. HIV/AIDS treatments in the form of ARVs were originally developed with wealthy consumers in mind. Those treatments have now spread to poorer countries which are most affected by the disease, but are unable themselves to bear the cost of R&D for such treatments.

Statins are also an increasingly important tool in the fight against cardiovascular diseases in lower-income countries, with many of these powerful drugs now off-patent and open to generic competition. Again, these treatments originated – and are still being developed – in wealthier countries under the current commercial R&D paradigm.

Nonetheless, research and development into the diseases of poverty is far from moribund. Dr. Mary Moran of the London School of Economics (LSE) found that activity in this area had reached unprecedented levels by the end of 2004. This largely is due to the formation of new neglected disease institutes which are operated by pharmaceutical companies and the creation of new drug development Public Private Partnerships (Moran et al., 2005). Moran notes that:

> "There were 63 neglected-disease drug projects under way at the end of 2004, including two new drugs in registration stage and 18 new products in clinical trials, half of which were already at Phase

> III. Assuming there is sufficient funding, at standard attrition rates these projects would be expected to deliver eight to nine new neglected-disease drugs within the next five years, even if no further projects were commenced after this time."

Furthermore, Moran and her co-researchers at the LSE expect this activity to increase in the future as some of the newer PPPs and institutes become more established. This is discussed in greater detail in Chapter 4.

Discussion

It is clear that the disease burden in poor countries remains very serious, reducing the potential for economic development. However, the evidence also suggests that if policies were instituted that enabled people to generate wealth, then many of the causes of diseases – especially a lack of access to clean water and poor nutrition – would be substantially reduced. Wealthier societies are also better able to afford medicines. In the long-term, then, pro-growth policies clearly are a part of the solution. In the short to medium-term, however, many actions can be taken that could reduce the disease burden substantially. For example, there are vaccines and medicines for many of the diseases that cause the greatest burden. Unfortunately, the mythical '10/90 gap' has distracted attention away from these readily available and inexpensive interventions. Even for those diseases for which existing cures are less effective, there are many new drugs in the pipeline that in the future could offer cost-effective cures.

2

Cost effective means of reducing the diseases of poverty

This chapter considers the cost-effectiveness of existing strategies for addressing the diseases of poverty promoted by the WHO and other organisations and compares these to other possible strategies. While not explicitly within the remit of the CIPIH, this section is included in order to put the issues discussed elsewhere into context.

HIV/AIDS: The WHO's '3 by 5' treatment plan

In September 2003, the World Health Organisation announced that it would ensure that by the end of 2005, 3 million HIV-infected people would be on anti-retroviral treatment. Since then, many billions of dollars have been spent attempting to achieve that goal. In June 2005, UNAIDS/WHO estimated that 6.5 million people in lower-income and transitional countries urgently needed ARV medication. Of these, only 970,000 people (15 percent) actually had access to these drugs. In sub-Saharan Africa, only 11 percent of those who needed treatment were receiving it (UNAIDS/WHO, 2005a).

Depressingly, the failure of the initiative was entirely predictable. The overwhelming majority of people living with HIV/AIDS are in sub-Saharan Africa, where public health systems are fragmented, dilapidated or nearly nonexistent. Most countries in the region lack qualified health workers and doctors, not to mention pharmacies, clinics and hospitals.

Antiretroviral drugs are complex to administer, requiring specified regimens and oversight by knowledgeable professionals and testing equipment, both of which are in short supply in most of Sub-Saharan Africa. Seen in this light, the WHO's decision to push its mass treatment initiative as the key to solving the AIDS crisis was a gross strategic error. Without sufficient staff and facilities, there is a substantial risk that inappropriate doses will be handed out to patients, and patients will not adhere to regimens. This raises the spectre of resistance, which has the potential to render many of the currently available treatments ineffective (Blower et al., 2003).

But much more is at stake here than the WHO's reputation. In its desperation to increase the number of people on the drugs, the WHO also advocated the use of untested triple drug fixed-dose combinations. In late 2004, safety concerns forced the agency to de-list these drugs (produced mainly by otherwise-reputable Indian drug companies) which further eroded trust in the programme.

The UN's own statistics indicate that more people became infected with HIV in 2005 than ever before, with an estimated additional five million new infections worldwide. The number of people living with HIV globally has also reached its highest level ever, with an estimated 40.3 million people, up from an estimated 37.5 million in 2003 (UNAIDS/WHO 2005a). Over three million people died of AIDS-related illnesses in 2005; of those, more than 500,000 were children.

This unprecedented rise in the number of AIDS sufferers is in part the result of the WHO's prioritisation of treatment over prevention. Leading public health experts are virtually unanimous in concluding that prevention is of paramount importance in the fight against AIDS (Salomon et al., 2005). Moreover, most African countries lack the health infrastructure properly to administer and monitor ARV treatment. By betting the house on

treatment, however, the WHO has seen new cases pile up quicker than they can be treated.

But the WHO is not alone in promulgating such strategic errors. The US Congress has required that the President's Emergency Plan for AIDS Relief (PEPFAR) should dedicate 55 percent of the US $15 billion five year budget for HIV on treatment of individuals with HIV/AIDS. In financial years 2006 through to 2008, 75 percent of this is to be spent on the purchase and distribution of antiretroviral drugs, with only 20 percent of all funding to be spent on prevention.[5]

Education is central to prevention. In Uganda, one of the few countries in sub-Saharan Africa where HIV prevalence has fallen in the past decade, education played the key role. The country's ABC programme ('Abstain, Be faithful, or Condomize') emphasised the risks of casual, unprotected sex, and has had a dramatic effect on patterns of sexual activity, contributing to an 80 percent reduction in HIV prevalence (Singh et al., 2003).

Even if HIV prevalence is brought under control, we are still left with the issue of how best to distribute antiretroviral drugs to infected patients. A remarkably successful public private partnership in Botswana between the Gates Foundation, several western drug companies and the government offers some lessons. This initiative involved the construction of clinics to distribute high-quality antiretrovirals, while schools and colleges have undertaken public education programmes (Ramiah & Reich, 2005). Botswana now has more people on ARV treatment than any other country in sub-Saharan Africa and is the only such country to provide free treatment for all.

Private philanthropy can be an effective stop-gap measure. In the medium to long term, however, Africa needs self-sustaining, efficient health-care systems that allow effective distribution of life saving medicines, as well as the propagation of vital health education.

Malaria

In order to combat the global malaria problem, the WHO and associated agencies kicked off an ambitious plan to 'Roll Back Malaria' (RBM) in 1998, with the goal of halving malaria incidence by 2010. It proposed to achieve this by a combination of judicious use of medicines and the distribution of insecticide-treated bed nets.

Seven years in, there are some indications that the global malaria problem is not improving and may be getting worse. Although problems associated with collecting accurate data make it difficult to determine precisely how many people suffer from malaria, in 2002 an external evaluation of RBM set up by the WHO said:

> "Anecdotal evidence and the strong consensus among experts suggests that, at the very least, the malaria burden has not decreased. What is more likely, and believed to be the case by most of those involved, is that malaria has got somewhat worse during this period." (Malaria Consortium, 2002)

More recently, scientists from the University of Oxford suggested, on the basis of improved measurements, that more than half a billion people – nearly double previous estimates – were infected by the deadliest form of malaria in 2002 (Snow et al., 2005). Clearly, the Roll Back Malaria campaign is failing to achieve its stated goal.

But the real tragedy is that malaria might be far less of a problem today if the WHO had adopted a different strategy from the beginning. An important part of such a strategy would have included spraying the inside walls of residential buildings with insecticides such as DDT. Remarkable control was achieved in the 1950s and 60s, even in regions where transmission rates were unusually high. But since the cessation of such activities the disease has returned to many such areas, often with devastating impact on human mortality. Residual treatments are far more effective than using bednets, but have been rejected because of environmental concerns. Such indoor residual spraying (IRS) helps prevent mosquitoes from entering dwellings and it repels or kills those insects that do manage to enter. Because it minimises the chances of humans being bitten, IRS effectively prevents the

transmission of the malarial parasite, which makes it an excellent tool for preventing the spread of the disease. In the years following World War II, the WHO put DDT at the centre of its malaria eradication plan, saving an estimated 50 to 100 million lives through prevention alone (Roberts et al., 1997).

Many countries have tamed malaria through IRS with DDT (Roberts et al., 2000). India, for example, started a nationwide programme of IRS with DDT in the 1960s. In that decade, India deployed around 18,000 tonnes of DDT and reduced malaria cases from 75 million per year to less than 100,000. Unfortunately, the caseload increased significantly when the use of DDT was reduced in subsequent decades (Sharma, 1987).

More recently, Namibia, Botswana, Mozambique and South Africa have been somewhat successful in reducing the incidence of malaria through IRS programmes utilising DDT and alternating with other pesticides (Baird, 2000). Uganda is determined to utilize this powerful tool, despite potentially being threatened with trade sanctions by the EU.[6]

Over the last few decades, however, the WHO has discouraged the use of DDT in member states – encouraged by environmentalists, who have often massively overstated the negative effects of DDT on human and animal health (Roberts et al., 2000). Until recently, most Western aid agencies discouraged the use of DDT and indoor residual spraying generally, and the WHO has provided little financial assistance to those governments that wish to go down this route.

Recently, however, USAID has re-evaluated its support of IRS, deciding to allocate more funding to such projects. The WHO also undertook something of a *volte face* in November 2005, when it announced that IRS with DDT would form a key plank of its Roll Back Malaria programme.

In terms of prevention, the WHO's Roll Back Malaria strategy has largely focused on the distribution of insecticide treated bednets, claiming that they provide the most effective means of vector control. It funds bednets almost to the exclusion of other preventative measures.

While bednets may have a role in preventing transmission of malaria (Premji et al., 1995; Philips-Howard et al., 2003), they are far from perfect, particularly in the poorest areas where they are most needed but can only be obtained at considerable expense. Mosquitoes tend to be most active in the hottest parts of the year, and few people relish the thought of covering themselves in a net during these hot nights. In certain parts of Africa, people are reluctant to sleep in nets because they resemble a shroud. People also often misuse bednets, with enterprising individuals using them as fishing nets. Even when bednets are used properly they are a far from perfect barrier, not least because mosquitoes, being opportunistic, will take advantage of any occasion when a person happens to get out of bed during the night (Bean, 2001; Choi, 1995).

Bednets also face the hurdle of effective distribution. While public health authorities in many parts of Africa find it difficult to distribute routine and simple vaccines and treatments, so too are they failing to get the nets out to all people who need them. These problems are compounded by the fact that the nets need to be retreated with insecticide every three months, or else they lose much of their utility.[7] According to one study, fewer than five percent of children in malarial areas currently sleep under a bednet (Hamel et al., 2001).

Indoor residual spraying alone is not enough. The most successful malaria control strategies have been those which have combined indoor spraying with education campaigns to encourage people to eliminate breeding sites, such as used tires which can collect stagnant water, and changes in the management of animals in order to reduce the proximity of these malaria parasite reservoirs to people.[8]

In combination with these strategies, prophylactic drugs can play an important role in reducing the pool of malaria parasites in the human population and thereby reduce transmission rates. This is especially important for the most deadly species of human malaria parasite, *Plasmodium falciparum*. In addition, effective drug treatment can help to reduce the number of deaths.

However, the WHO has also mishandled treatment recommendations. Until as recently as 2004, it advocated the use of chloroquine in Africa, even in the face of increasing resistance to that drug by the *P. falciparum*. This was despite the existence of a far more effective – albeit more expensive – alternative, Artemisinin Combination Therapy (ACT). In fact, the WHO recognised the benefits of ACT and named it a central plank of its RBM strategy, only then to approve the use of the nearly useless chloroquine in many African countries because it is cheaper (Attaran, 2004). The WHO only recently started heeding its own advice and properly approving ACT after it came under pressure from malaria experts and the international press. But in part because of the abruptness of WHO's belated change in strategy, artemisinin supply is now unable to keep up with increased demand.

Clearly, the availability of appropriate and effective medicines is of great importance to helping those already infected with the malarial parasite. However, sensible and wide-scale prevention techniques could remove much of the need for medication, largely because there would be far fewer infections in the first place. Reducing the prevalence of malaria would then free up considerable resources for the purchase of the most effective, modern medicines and avoid debacles such as occurred with RBM and chloroquine.

Diarrhoeal diseases

Diarrhoeal diseases are one of the major causes of premature childhood deaths in lower-income countries. According to the World Bank, three million children die every year from cholera and other water-borne diarrhoeal disorders (World Bank, 2002). Much suffering could be averted with effective use of treatments such Oral Rehydration Therapy (ORT). In addition, antibiotics could be used to eliminate more serious bacterial infections. Finally, vaccines have been and are being developed against viral causes of diarrhoea, such as rotavirus; if these vaccines were deployed widely, the incidence of such diseases could be reduced dramatically. In the case of rotavirus, a vaccine could prevent some 500,000 childhood deaths annually.[9] Unfortunately, at present even inexpensive treatments such as ORT do not reach those most in need (Rao et al., 1998).

Another, more fundamental approach to controlling these diseases focuses on improving the quality of drinking water. Currently, water resources in most countries are owned and controlled by the state (typically municipal governments). Yet in poor countries, the state has shown itself to be a very poor provider of water, with some respite from dry or non-existent taps being provided by informal private suppliers (Okonski, 2006). Where ownership and/or management have been transferred to the private sector, access has typically improved considerably, as has been shown for Chile (Rosegrant & Gazmuri, 1994), Argentina (Galiani, Gertler & Schargrodsky, 2003) and Guinea (Menard and Clarke, 2000; Noll et al., 2000; Brook Cowen, 1999). In Argentina, in particular, there is strong evidence that privatisation of supply has led not only to improved access but also to reduced incidence of water-borne disease, especially in the poorest districts (Galiani et al., 2003).

Finally, much could be done to improve sanitation in poorer countries, including improvements in sewerage. In addition, this means educating people to use soap and other cleansing agents. Such education could in principle be provided by the private sector – for example, by companies who have a material interest in selling soap – but this is often inhibited by a political environment hostile to commercial enterprise.

Acute lower respiratory infections

Another major contributor to premature deaths in lower-income countries is acute lower respiratory infections (ALRI). One of the leading causes of such infections is inhalation of smoke from dirty energy sources such as wood, dung and crop residues burnt in poorly ventilated dwellings. Exposure to such smoke increases the risk of ALRI (such as pneumonia), especially in children and women. This problem afflicts up to half of the world's population, almost entirely in the poorest countries. Globally, ALRI represent the single most important cause of death in children under five years of age, and

contributes to approximately two million deaths annually in this age group (Bruce et al., 2002).

Thus, if the poor were able to use more efficient, cleaner forms of energy, the positive impact (in terms of reducing the global disease burden) would be immense. Unfortunately, governments tend to restrict the ability of people to use cleaner fuels and technologies such as electricity, liquefied petroleum gas (LPG) or even kerosene. The impact of these restrictions falls primarily affects poorer households, who must then resort to burning wood, low-grade coal, crop residues and animal dung, which in turn exacerbates both indoor and local air pollution.

In India, for instance, the country's 2001 census revealed that less than 44 percent of households have an electricity connection (Goswami, 2004). Because the national and state governments have intervened extensively in the supply of electricity, the country has an artificial shortage – so merely possessing an electricity connection does not mean that a household actually receives electricity.

Policies of the Indian government have also contributed heavily to a shortage of petroleum-based fuels in the country, which particularly affects the rural poor. Kerosene is subject to government rationing. Only two government-run companies in India supply LPG – thus, these companies are not competing in a dynamic, competitive market. Although LPG production is in principle subsidised by the state, it is unclear whether these subsidies are passed on to consumers (in the form of lower costs) or whether the companies inflate their production costs (thus absorbing the subsidy). Moreover, there is little if any distribution network for LPG – so private suppliers are unlikely to enter the market. This explains why rural access to LPG is extremely low; India's 2001 census revealed that fewer than 10 percent of rural households utilize LPG (Goswami 2004).

These examples show why government policies towards can have harmful side effects for health – contributing directly or indirectly to the prevalence of ALRI in poor countries such as India.

While prevention is almost certainly preferable to cure, there are also many inexpensive medicines that can be used to treat pneumonia and other ALRI. However, these often are not available – for reasons that are discussed in Chapter 3.

Diseases associated with malnutrition

Poor nutrition contributes to 53 percent of deaths associated with infectious diseases among children under five years of age in lower-income countries (Black et al., 2003). Many cases of malnutrition could be prevented if people were able to produce and distribute food more efficiently, yet in Africa especially this has been difficult because of weak property rights.

In agrarian communities, strong property rights enable more efficient farming practices. First, the ability freely to buy and sell land means farmers are better able to achieve economies of scale. Second, clearly defined property rights enable land owners to access low-cost capital, in the form of mortgages, that otherwise would not be available. Such loans enable people to invest in more capital-intensive forms of production, both on farm and off. The result is higher yields, greater investment – and profit from – non-farm forms of economic activity, and generally an increase in wealth.

In addition to improving the efficiency of agricultural production, many technologies exist that could help improve this situation. One such technology — biofortification — entails breeding specific traits into a plant such that it produces and contains essential micronutrients that can be utilized by the human body.

One example of biofortification is Golden Rice, which was developed as a humanitarian project to address Vitamin A deficiency. This deficiency kills at least 6,000 children every day and leads to irreversible blindness in 500,000 children each year (WHO, 1995). Traditional interventions such as the distribution of vitamin A capsules by the WHO are helpful but have not substantially reduced these figures.

In 1999, a 15-year project culminated when two teams of European scientists successfully modified the starchy

tissue of rice (the part consumed by humans) to produce pro-Vitamin A (the chemical that is converted into Vitamin A in the body).

However, activists who are opposed to GM foods more generally objected that the fortified rice, when eaten in normal quantities, would not provide a poor person with the necessary levels of dietary Vitamin A. However, a new strain of the rice (Golden Rice II) has been developed that would provide 23 times more pro-Vitamin A compared to Golden Rice I, effectively solving this problem (Paine et al., 2005).

Since 1999, the inventors of Golden Rice have sought to transfer the benefits from this technology to the poor in lower-income countries – e.g. the people for whom it was intended. Governments and charities were able to finance the entire project research, but not the subsequent development and regulatory stages. Attempts to take Golden Rice to its next phase, with field trials and tests for nutritional compatibility in individual countries, have been thwarted by an overly precautionary approach by regulators, fuelled by the sentiments and actions of activists. The same fate befalls many other genetically modified crops (Paarlberg, 2006).

The field trials have been delayed because opponents of Golden Rice insist that the plants must pose no risk to the environment. For humanitarian projects, such barriers create unnecessary expense and delay. This is not to suggest that Golden Rice should be exempted from normal regulatory procedures. The problem is that regulators have focussed on hypothetical and mostly non-existent risks rather than reasonably assessing the actual risks alongside the real benefits, in particular, the potential to immediately reduce Vitamin A deficiency and thereby save human lives. As a result, researchers will be less inclined to use biofortification to solve other micronutrient problems — such as iron, protein and zinc deficiency.

Discussion

In tackling diseases of poverty such as malaria and HIV/AIDS, global public authorities such as the WHO have a track record of prioritising grandiose but unachievable schemes over more practical approaches. Billions of dollars have been spent in recent decades, with little discernible impact on mortality rates.

In the context of HIV/AIDS, intervention by the WHO seems to have exacerbated the problem by neglecting prevention in its aspiration to achieve 'treatment for all', with the result that new infections are soaring.

In the context of malaria, public health experts have long advocated indoor residual spraying with insecticides such as DDT, yet the WHO and aid agencies have until recently provided little practical support for those nations wishing to adopt this practice. The failure to date of the WHO's Roll Back Malaria programme also reveals the limitations of the argument that intellectual property rights are standing in the way of improving human health. The price of patented drugs has little (if anything) to do with the failure of public health agencies to reduce the impact of the disease. RBM failed because WHO was responsive to special interest groups whose concerns seemingly had no relationship to actions which would actually improve the lives of the poor.

The burden of both HIV/AIDS and malaria could be significantly reduced with sensible prevention strategies and careful treatment programmes. While new medicines for these diseases would obviously be beneficial, in order to address the inevitable development of resistance to available treatments, we must recognize that effective distribution of those treatments will be practically impossible until the physical and human aspects of health infrastructures are improved.

The cases of ALRI and diarrhoea reinforce the fact that there is a need for greater focus and more appropriate strategies in tackling all the diseases of poverty. We believe, in particular, that policies pursued by intergovernmental agencies, national governments, and humanitarian charities would benefit from an improved understanding of the root causes of extreme poverty and ill health. In this regard, a growing body of literature implicates corruption, weak or non-existent rule of law and limits on economic freedom (see e.g. Greenspan, 2003; Gwartney & Lawson, 2004; Kasper, 2006). The

reform of governance structures must therefore be a priority; that means strengthening property rights, liberating markets and entrenching the rule of law.

Admittedly, the reform of governance in sovereign states is outside the bounds of WHO policy. But the fact that so many African governments are corrupt and ineffective does not excuse the WHO from promulgating the disastrous strategies it has followed. Indeed, the very fact that health infrastructure is so weak in the world's poorest countries makes many of these strategies all the more absurd.

3

Increasing access to medicines

This chapter examines some of the factors that prevent existing medicines from being distributed in the most effective manner. We begin with a description of the major barriers to access, which include weak healthcare systems, taxes on imported medicines, and poorly functioning insurance markets. We then examine several related issues, including the impact of poor government policy on the supply of medicine, the role of intellectual property, and the impact of pre-market regulations and price controls.

Weak healthcare systems

Healthcare systems and associated infrastructure are vital for the effective distribution of medicines. If healthcare systems are starved of resources, it is unlikely that they will be able either to procure necessary drugs or be able to employ sufficient numbers of doctors and other trained personnel necessary to prescribe and administer medicines.

The majority of low-income countries lack the basic infrastructure required to distribute medicine successfully. Road networks are often unreliable or non-existent, making it difficult to ensure a constant supply of medicines to remote areas (Saleh & Ibrahim, 2005). Electricity is often unavailable, especially in rural areas; where it is available, it is often supplied in an erratic fashion. This increases the cost and difficulty of running refrigeration systems in clinics and hospitals. As a result, vaccines are often not maintained at sufficiently low temperatures to ensure product stability. Protease inhibitors (used in second-line ARV treatments) are one example of a drug that needs to be refrigerated (Kumarasamy, 2004), yet due to erratic power supplies and other issues, it is impossible to ensure constant refrigeration in the world's poorest countries.

In this situation, it is extremely difficult to ensure the distribution of the safe and effective medicines that have already been developed to tackle the diseases of poverty. For example, a relatively effective treatment for tuberculosis is Directly Observed Therapy Short Course (DOTS), which requires between 6 to 8 months with close patient monitoring to ensure compliance. ARV treatment for AIDS sufferers also requires close supervision over the lifetime of the patient. Even in the relatively efficient health care systems of high-income countries, maintaining adherence to HAART (Highly Active Anti-Retroviral Therapy) treatment during clinical trials is fraught with complexity (Kumarasamy, 2004). Achieving such adherence in poor countries with weak health care systems is practically impossible.

Intervention by global public health authorities and the provision of public funds is not a guarantee that existing medicines will be effectively distributed. Consider the example of malaria, discussed in Chapter 2: despite the establishment of the Roll Back Malaria initiative and the injection of specific funds, the most modern and potent anti-malarial drugs were still not being correctly used six years after the initiative began (Attaran, 2004).

Weak healthcare systems do not simply result in a failure to distribute existing treatments. They also have a knock-on effect for the demand for new drugs, and can act as a serious disincentive to would-be innovators of new medicines. If a product is unlikely to reach its intended market, what is the point of developing it in the first place? Well-equipped and properly staffed modern medical facilities are adept at disseminating the latest

Case study: How the South African health system hinders access to medicines

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The experience of the South African public health system offers some insights as to why 20 percent of the country's population is unable to access essential medicines (UN, 1999).

At the outset it should be made clear that there are two distinct and separate health sectors in South Africa. The dichotomy is largely a hangover from past policies formulated under the apartheid regime. On the one hand the private health sector provides a world-class health service, with excellent facilities, advanced technology, well-remunerated staff and good access to all medicines. On the other hand the public sector is plagued with inefficiency and for the most part South Africa's public health care system struggles to meet the needs of the patients it is supposed to be serving. The result is that patients seldom receive the level of care that they deserve.

The South African government receives medicines at substantially reduced costs from large multinational pharmaceutical companies. However, historic and ongoing lack of infrastructure, personnel and poor logistics means that frequently the medicines do not reach those for whom they were intended. Furthermore, those that do have access to public sector health facilities usually end up queuing for hours, and are often turned away, trying to get even the most basic medicines. Not surprisingly, in 2000 the World Health Organisation (WHO) ranked South Africa's health-care system 175th out of the 191 member countries.

There is also a great deal of theft in public hospitals. For instance, in Mpumalanga province, 46 medical professionals ended up behind bars in the first two months of 2003, charged with the theft and resale of government medicines meant for the rural poor in Mpumalanga. Those arrested included a manager of a rural hospital, doctors, pharmacists and medical technicians as well as a syndicate of 'bag men' who delivered stolen drugs, including birth control pills, pain killers and antibiotics, to private doctors.

The medicine shortages caused by the syndicate's medicine thefts reportedly prevented routine operations from being performed, and complicated the day-to-day treatment of patients at the Rob Ferreira and Themba hospitals in Nelspruit, the capital of Mpumalanga.[10] The extent and nature of theft and corruption in the public health system reinforces the severe shortcomings in hospital management, administration and control systems.

The South African drug regulator, the Medicines Control Council (MCC), is notoriously inefficient and tardy with its approval process. On average, drugs that have already been registered for use in the US, EU and Japan can wait for 39 months to be approved by the South African system. A further barrier to access in South Africa is Value Added Tax (VAT). The SA government continues to charge VAT on pharmaceuticals despite the fact that the tax is highly regressive since it disproportionately affects the poorest members of society.

If the South African government is serious about increasing access to medicines to the poorest of the poor, then they will waive VAT on all medicines. VAT is counter-intuitive in the sense that if one of government's primary objectives is to have a healthy and productive workforce, surely it does not want to tax the sick and vulnerable. The VAT received by government on pharmaceuticals is relatively insignificant. However sick people could use the money that would have been spent on VAT for a number of beneficial alternatives, including food.

According to the latest estimates by the official government statistical agency, Statistics South Africa (SSA), approximately 26 percent of the South African labour force is unemployed. If discouraged work seekers are also included, this figure jumps to approximately 41 percent. The consequence of mass unemployment is that there are large numbers of individuals that currently live in extreme poverty. Indeed, it is estimated that there approximately 5 million people in South Africa live on less than a dollar a day. Therefore, it is not unreasonable to assume that many of them simply cannot afford to buy even basic pharmaceutical drugs. While the government claims to take responsibility for the health care of the indigent, it is obviously not capable of meeting unlimited demands.

How do we remedy this situation? In the long run, the only way to increase access to medicines is through increasing the wealth of the citizens of a country and this is only possible through economic growth. In the short term, the government can substantially improve its distribution of drugs by privatising the distribution process and reduce waiting times by simply approving drugs that have already been approved for use in developed countries. Finally, the South African government's preferred policy of price controls will not increase access. On the contrary, it will simply reduce supply by eroding the incentives of potential suppliers.

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medical tools and drugs (Dussault & Dubois, 2003). Conversely, inefficient distribution and communications channels have an adverse effect on the speed with which new medicines reach patients, if they reach them at all (Gambardella et al., 2000).

Frequently, public spending and foreign aid injections into national health systems do not translate into the delivery of services and medicines to the poor. A multi-country study by Filmer and Pritchett (1999) showed that public spending on health in lower-income countries has only a minute impact on mortality. The authors showed that a significant proportion of deaths of children below five years could be averted for as little as US $10 each, yet even in the poorest countries, the average amount spent by governments per child death averted is a staggering US $50,000–$100,000.

There are many reasons for this low level of performance. First, public health agencies tend to be woefully inefficient and corrupt, especially in lower-income countries. As a result, the proportion of a donor's contribution that actually results in delivery of healthcare services (whether they are vaccines or nurses' salaries) is often very low. Health officials may sell aid-financed drugs on the black market. Studies in Guinea, Cameroon, Uganda, and Tanzania estimated that 30 to 70 percent of government drugs disappeared before reaching the intended patients (Filmer, Hammer & Pritchett, 2000).

Second, social programs nominally targeted at low-income groups are frequently captured by the articulate and influential rich (Deolalikar, 1995; Castro-Leal et al., 1999; Barat et al., 2003).

Third, public funding and provision can crowd out private funding and provision of healthcare. If a government starts to provide a good or service for 'free', this is a clear signal to private providers to exit the market. The net amount of healthcare provided may remain constant — but where there was once diversity of provision, there is now an effective monopoly, which has its own efficiency problems. As a result, public funding and provision typically has little to no impact on actual health outcomes (Filmer, Hammer & Pritchett, 2000).

Taxes and tariffs

Many governments of lower-income countries compound the problem of weak healthcare systems by imposing a range of taxes on medicines, including port charges, central, regional and local taxation, as well as import tariffs and VAT. Other government-imposed measures or regulations may include pre-shipment and inspection costs, and pharmacy board fees. Taken together, these add significantly to a drug's retail price, with negative consequences for access to medicines, especially for the poorest.

Why do governments tax medicines?

Given the massive negative impact of local price inflators on the cost of medicines for the poor, it must be asked why governments choose to implement such policies. There are two main reasons: to protect local industry and to raise revenue.

Protection of local industry. In some cases, policies are designed to protect domestic industry, without little if any regard for how this may affect citizens. Both Levison (2003) and the European Commission (2003) observe that Nigeria, Pakistan, India and China all have significant local industries and are included in the group of countries with the highest import duties. Opponents of tariff removal support this policy, suggesting that reducing or abolishing tariffs could undermine the domestic industry which relies on high import barriers to survive. This argument is somewhat tenuous, as very few low-income countries – other than those listed above – have indigenous pharmaceutical industries of any significance. At any rate, industry protection via tariffs often leads to entrenched inefficiencies and results in expensive, poor quality products.

Income Generation. Taxes and tariffs generate revenue for the government. In some very poor countries, import tariffs in general represent an important source of income for governments where collection of other sorts of taxes is difficult. However, tariffs on medicines are rarely a significant source of revenue.

In a survey of nine countries, Levison and Laing found that that costs resulting from government policy or regulation added an average of 68.6 percent to the cost of imported pharmaceuticals (Levison & Laing, 2003).

Taxes and tariffs under the microscope

Tariffs are often a particularly important factor in determining the end-user price of pharmaceuticals in low-income countries (Bate et al., 2005). A 57-country study conducted on behalf of the European Commission in 2003 examined taxes and tariffs on pharmaceutical products used in the treatment of communicable diseases.[11] The study found that the countries that apply the highest tariff rates include Nigeria, Pakistan, India and China (European Commission, 2003). As a result, large sections of the populations of these countries are being priced out of treatment by their own governments.[12]

Another disturbing government levy on pharmaceuticals is value added tax (VAT). VAT is a revenue-raising instrument that can exist at several levels of the political system, and may be applied to different classes of products, or certain sectors (Levison & Laing, 2003). The European Commission (2003) found that VAT was imposed on pharmaceuticals at average rates of over 12 percent.

Taxed to death in East Africa

A recent example of a tariff regime raising the retail price of medicines in poor countries comes from the East African Community Customs Union.[13] From January 2005, all ready-to-use generic and branded medicines entering Uganda, Kenya and Tanzania have been taxed at a rate of 10 percent. [14] Since most distributors were previously supplying the market at cost, the tax (estimated at approximately US $20 million for Kenya and Uganda) was expected to be passed straight onto patients (Kimani, 2005).

There are also cases of the tax being applied to freely donated drugs, as in the case of the US $3.1 million worth of insulin donated to Eldoret's Moi Teaching and Referral Hospital in Kenya by Eli-Lilley.[15]

Table 2 **Duties and taxes on retail medicines**

Country	*Combined total duties and taxes*
India	55%
Sierra Leone	40%
Nigeria	34%
Pakistan	33%
Bolivia	32%
Bangladesh	29%
China	28%
Jamaica	27%
Morocco	25%
Georgia	25%
Mexico	24%

Table adapted from European Commission (2003)

Table 2 shows the combined impact of taxes and tariffs (customs duty + VAT + other duties) on the retail price of medicines in selected poor countries. The global average is 18 percent, with Malaysia having the lowest rate (0.01 percent) and India the highest (55 percent).[16]

By driving up the cost of medicines, these taxes and tariffs price the poorest people out of the market for life-saving treatments. They are regressive because they adversely affect the poor and the sick. Such government policies effectively impose a wedge between the demand for drugs and their supply. In markets where profit margins are already low, drug companies have fewer incentives to supply their existing products, much less to innovate new products specifically aimed at these markets. As Levison (2003) observes: "Economically…tariffs impede the action of a competitive market where the best drug will achieve the best price and [they] protect inefficient [local] producers who charge high drug prices." (Appendix Figure 2 shows how taxes restrict the demand for medicines.)

Non-tariff barriers

Beyond visible barriers such as tariffs, manufacturers wishing to export to overseas markets often face

significant hurdles and complexity in registering their products. These tend to emanate from local drug approval agencies, and often appear to be designed to protect local industry rather than achieving better outcomes for patients. Some examples of such non-tariff barriers are the following:

- *Harmonisation*: Certain countries are guilty of requiring importers to attain standards higher than those required by relevant trade bodies, often without any scientific justification.
- *Transparency*: Many countries fail to provide adequate information regarding the regulations and procedural norms concerning methods of sampling, inspection and testing of drugs. New regulations are often introduced without giving the producers in exporting countries an opportunity to understand and/or comply with those regulations. Often the standards are available only in the language of the importing country or are presented in a very complicated manner. As a result, exporters lack clear guidance about the specific requirements, which can lead to rejection at the point of import.
- *Conformity assessment issues*: Importing countries may require testing to occur at a single location which may be at an inconvenient location, adding an additional burden of cost and time. Certificates may have limited validity, requiring frequent re-testing, while on occasion importing countries may not recognise the certificates of international bodies.
- *Marketing restrictions*: Often, importing countries require their own standard of labeling on products, which can be cumbersome to exporters from lower-income countries who are trying to export to a range of different countries, all with different criteria.
- *Restrictions on port of entry:* Several countries allow imports only through designated ports, which increases transit times and transaction costs.

One example is South Africa's Medicines Control Council (MCC), which requires that all new medicines must attain its own regulatory approval before they can be marketed in the country – even if they have already been approved by reputable foreign regulatory bodies such as the US FDA. However, the extreme inefficiency of the MCC means that drugs which have already been registered for use in the US, EU and Japan wait an average 39 months for approval in the South African system.

Another example comes from Namibia, which announced in 2002 that all medicines registered in the country prior to independence (1990) should be re-registered (Bate et al., 2005).

The low purchasing power of the majority of citizens in poor countries means they do not constitute significant markets for foreign manufacturers. In the face of such non-tariff barriers, companies will often forego the regulatory complexity and expense of registering their products in that country (and will instead invest their resources elsewhere). The result is that fewer medicines are approved — even when they are desperately needed — and there is a lower level of local competition in the marketplace which would otherwise drive prices down and increase access.

To make matters worse, many governments now adopt the WHO's list of 'essential medicines' as the basic formulary, denying their citizens access to medicines not on the list (see box on p. 32).

Inadequate health insurance

Health insurance enables individuals to pool their financial resources and thereby protect themselves against the risk of unexpected and expensive illness. In return for monetary payment, an insurer agrees to compensate the individual in a specified way should defined, uncertain events actually happen.

When health insurance systems function well, demand for healthcare increases because larger numbers of people are covered against the costs of ill health. Several studies have shown the link between greater uptake of therapeutic medicines among poor and vulnerable populations, and the availability of health insurance in the United States (Department of Health and Human Services, 2002; Poisal & Chulis, 2000). However, many low-income countries do not have properly functioning health insurance schemes. In 1998 not one low-income

WHO essential medicines list

Dr John Kilama, Director, Global Bioscience Development Institute

If poor people in the U.S. and the EU had access only to the limited range of options on the World Health Organization's Model List of Essential Medicines (EML), most doctors would denounce that situation as unacceptable. So, too, would most healthcare workers in other developed countries around the world. Why then has no one questioned the rationale behind the WHO's List of Essential Medicines – frequently the authority that dictates the drug selection process for many health Ministries in poorer countries?

The WHO EML represents the most comprehensive international compilation of essential medicines for public health. The list was compiled beginning in 1975, in the wake of World Health Assembly's decision to focus on high quality, reasonably priced essential medicines. Since it was first published in 1977, the WHO EML has ostensibly aimed to provide for the majority of people worldwide affordable, safe and effective medicines for most of their health needs.

The first model list identified 208 individual drugs and since then multiple deletions and insertions have been made. Drugs can be removed from the list if their safety is found to be questionable following the appearance of new data.

Despite this, the concept of the EML is ill-fitted to the myriad health needs of people in lower-income countries. Diseases such as diabetes, hypertension, cancer, cardiovascular disorders, gastrointestinal disorders, dermatological disorders and arthritis are just as common in Africa as in developed countries. Yet the WHO Essential List of Medicines does not provide medical practitioners in Africa with sufficient choice for dealing with these diseases.

Medical practitioners are well aware that each individual responds to medicine in a unique way. An anti-anginal medicine such as Verapamil produces a range of different results in any given population. It may not work in one individual who suffers from anginal disorder yet it may produce good results in another individual who has very similar symptoms. So why recommend only a few products as 'essential' if we know that different people respond differently to the very same drug product?

Unfortunately, in Africa, if your disease cannot be treated with any of the drugs on the WHO List of Essential Medicines, you are simply out of luck. You need to go outside the essential list to get relief, but that may not be possible. Most African health ministries have adopted the WHO guideline as their approach to healthcare, making it all but impossible to obtain the most appropriate drugs. This approach is irrational, and is not good for public health.

The African healthcare crisis extends beyond the highly publicised problems of HIV/AIDS and malaria. Although the international community has paid little attention, hypertension and diabetes are also widespread in Africa, and the combined number of deaths from those two diseases nearly equals the toll from HIV/AIDS.

When it comes to treating those diseases, however, Africans have limited options. Even those who can afford drugs that are not on the EML do not have the opportunity to do so. That is because most African governments allow the importation of only those drugs that are on the list. When it comes to drugs for hypertension, for example, there are only six drugs on the WHO list. If one of those six listed drugs cannot control an African's hypertension, he or she will die because no other hypertension drugs are registered for sale in that country.

The disease burden in lower-income countries is coming increasingly to resemble that of higher income countries, especially in terms of cardiovascular diseases and cancers. Plenty of new drugs are coming on stream to combat these diseases, but the rationale behind the EML denies patients in poorer countries access to these new drugs. This is because the EML deliberately favours listing generic medicines over patented ones. In this way, the treatments available to patients in poorer countries do not match the contours of the disease burden. This also discourages innovation, as the EML sends confusing and inaccurate signals with regard to which diseases are most prevalent at the local level.

Tensions are mounting. In Kenya, a dispute has broken out between those who import essential medicines and those who want to import brand name drugs, of which generic copies are sold in Kenya. Importers of 'essential' medicines on the WHO list do not want brand name drugs to be imported because importers are afraid of competition. They know there is a vibrant market for these drugs, which poses a threat to their commercial interests.

A more fundamental question must also be considered: Why even define some drugs as essential and not others? All drug products are essential to those people who need them. Each disease requires personalized treatment. Our goal should be to provide doctors with enough options to use exactly the right drug to fit the needs of each patient. Instead, the drug list seems to be designed to suit the needs of various vested-interests and pressure groups. As a result, the EML does not correspond with the actual demand for drugs on the ground.

country with a gross national product (GNP) per capita below US $761 had a social health insurance scheme (Carrin, 2002). Those individuals not covered by insurance pay for healthcare out of their own resources (or are nominally provided such services by the state). Since these people are already poor, their ability to purchase medicines – especially expensive medicines – is likely to be very low indeed. So the lack of availability of insurance acts as a significant barrier to access to medicines and constraint on demand.

One reason for the low level of insurance coverage in poor countries is the lack of adequate court systems and generally an absence of the rule of law, which makes the enforcement of legal agreements difficult, long-winded and expensive. Health insurance takes the form of a contract in which payment is made in advance of pay-out by the insuring company. In an environment where contracts are difficult to enforce, it is not surprising that many people are unwilling to risk paying into an insurance scheme. This specifically relates to a failure on the part of government to create an adequate rule of law and supporting institutions.

Another reason for low levels of insurance coverage in poor countries relates to the level of regulation placed upon private health insurers. For example, insurance companies may be required to offer certain kinds of insurance, regardless of whether or not consumers want the coverage. This is the case in South Africa, where the government has banned insurers from excluding high risk applicants, and compelled them to include cover that is not necessarily appropriate. The South African government is also working towards establishing a system that will require well-run funds to transfer their surpluses to badly-run funds. This latter intervention will limit the ability of actuaries to balance contributions against risk. Such regulations increase the costs associated with offering insurance, which increases the price at which it is offered. As a result, relatively fewer people are able to afford insurance. Paradoxically, regulations intended to protect consumers ultimately harm them (Soderlund & Hansl, 2000).

Governments also stifle the development of properly functioning insurance markets in less obvious ways. Weak governance structures, including poorly defined property rights, excessively bureaucratic rules for business, and an absence of the rule of law in many middle and low income countries mean that large sections of the population are forced to seek employment in the informal economy. The informal economy tends to be disjointed, which implies that it would be difficult for potential insurance companies to take advantage of economies of scale. At the same time, the diversity and transience of such workers and their dependents means that enrolment is difficult and costly, if not altogether impossible.

The International Labour Organisation estimates, for example, that between 1990 and 2000, 85 percent of all new jobs in Latin America were created in the informal sector. In Zambia, only 10 percent of the workforce is employed in the formal sector. Accordingly, in sub-Saharan Africa only around 25 percent of the work force is enrolled in health insurance schemes and most of those have been civil servants or employees of large multinational companies (Shaw & Ainsworth, 1995).

The size of the informal economy in many lower-income countries is directly attributable to weak governance. As Peruvian economist Hernando de Soto has convincingly argued, a lack of enforceable property rights and contracts, coupled with excessive regulation and bureaucracy, stifles the creation of legitimate employment opportunities (de Soto, 2001). A recent World Bank study found that, on average, it takes a business in a rich nation six procedures, 8 percent of income per capita, and 27 days to become legally recognized. In poor or lower-middle-income economies, by contrast, it takes an average of 11 procedures, 122 percent of income per capita, and 59 days. These relatively high costs mean that to a large extent, economic activity in such countries is informal. The same study found that weak property rights and heavy business regulation have an especially adverse effect on the ability of women and the poor to join the formal sector, despite the fact that such regulation is often designed to protect them (Wofford & Shanahan, 2004).

By presiding over such destructive governance, governments not only diminish the ability of their

citizens to create wealth, but also hinder the ability of functioning health insurance markets to develop. Without functional insurance markets, it seems unlikely that medicines will ever be available universally.

The lack of insurance has a knock-on effect on the potential market for drugs, acting as a disincentive to pharmaceutical innovation. Properly insured populations provide a stable and predictable market for medicines, reducing the investment risks of innovators. For those concerned about both access to existing medicines and the incentives to innovate new medicines, it is essential to ensure that effective insurance schemes are allowed to flourish. For this to happen, the regulatory environment needs to be as accommodating as possible. This should be a priority for policy makers who share these concerns. (Appendix Figure 3 shows what would happen to the market for medicines in poor countries if these demand-side barriers were lifted).

Barriers to innovation of new medicines

The absence of a functioning market economy not only keeps people poor and undermines access to and demand for medicines and other goods; it also directly affects the supply of medicines. Governments that fail to foster the rule of law discourage companies from supplying medicines in several ways. Slow, expensive and corrupt court systems make it difficult to enforce contracts, which in turn discourage potential suppliers from entering into supply contracts. Also, the risk that trucks carrying medicines will be stopped and the cargo stolen or impounded, or a bribe levied by corrupt law enforcement officers reduces the incentives of companies to supply medicines. In addition, difficulties enforcing trademarks mean that a company which attempts to market its products may find that it faces competition from cheaper – but typically less effective, ineffective, or even harmful – counterfeit products. The evidence suggests that judicial dysfunction impedes economic growth, and restricts the ability of inventors and creators to commercialise their inventions (Sherwood, 2000).

As such, these general institutional failures greatly reduce the incentives to develop new medicines, especially for diseases that primarily affect the poor. In addition, there are several specific issues in the institutions of many poorer countries that negatively affect incentives to develop new medicines.

Weak intellectual property legislation in low and middle-income countries

Some have claimed that patents create a barrier to access to medicines by increasing prices. While this is theoretically plausible, this scenario still does not explain the low rate of access to medicines that are already off patent and thus open to competitive, generic-based production.

It is true that when a state grants a patent, it provides the inventor with temporary exclusivity over the patent product or process. This can incur real costs, including the possibility to keep prices artificially high when, in absence of legal protection, market forces would drive prices down to their marginal cost – the lowest price at which a good can be sold without the producer making a loss. However, as Amir Attaran has shown, more than 98 percent of drugs on the WHO's 'Essential Medicines' list are not patented in any poor country. As we also illustrate in this report, there are many factors that conspire against access, but patents on these specific medicines are not one of them (Attaran, 2004). In any case, these criticisms of patent protection must also be weighed against their benefits.

When it comes to creating incentives to encourage the development of new medicines for the diseases of poverty, protection of intellectual property (IP) can play a crucially important role. The high cost of developing a new pharmaceutical product (estimated at upwards of $500 million in the US) (DiMasi et al., 2003), combined with the relatively low cost of copying the same product (typically a few millions of dollars), means that developers must be assured that they 'own' the product before they will commit such substantial sums.

Patents stimulate competition in several important ways that contribute to an environment in which new, better, more effective and efficient medicines replace older, less

effective and efficient ones. Importantly, this environment is also one where access to such innovations can be encouraged through mechanisms of markets.

One such mechanism is the provision of information about new medicines, through advertising and other marketing tools. By increasing demand for the medicine, such marketing sends a signal to other pharmaceutical companies that it may be worth investing in a competing product (For a more in-depth discussion about within-class and incremental innovation, see Chapter 5.)

More generally, IP protection in countries with incipient or extant knowledge-based industries is likely to spur economic growth, with positive consequences for the demand for medicines.[17] Weak IP laws enable the emergence of copy industries at the expense of innovator industries – with negative consequences for economic growth because the added value of the copy industries is typically lower than that of innovator industries.[18] In addition, innovator companies based in countries with strong IP protection will be less likely to engage in joint knowledge-oriented projects with firms in countries with weak intellectual property protection (Maskus, 2000).

It is perhaps not surprising, then, that between 1997 and 2001, 180 of the 184 new molecular entities were developed in the US, the EU and Japan,[19] where intellectual property protection is the strongest.

In addition to providing incentives to local companies to invest in the development of innovative products, IP protection in poor countries may spur innovation by foreign companies to serve local needs (e.g. developing drugs and vaccines to treat and prevent tropical diseases) (Lanjouw, 1998). By contrast, countries that exploit their weak intellectual property regimes by threatening to issue compulsory licenses for drugs reduce the incentives to invest in such research and development (Rozek, 2000).

The contrasting cases of India and Singapore shed some light on the link between strong intellectual property legislation and innovation.

In India, Indira Gandhi's government passed laws in 1972 that made it impossible to patent pharmaceutical products, with the result that the past 33 years have seen practically no new drugs created within that country to tackle its most pressing diseases. Instead, a large generics industry developed. Yet for all the copies of medicines being produced by India's then 20,000 or more pharmaceutical companies (many of them small-scale 'mom and pop' operations), access to medicines in India remained deplorably low, standing at less than 40 percent in 1999 (Lanjouw, 1998).

India's implementation of a TRIPS-compliant patent law has probably in part reduced the number of companies producing copies of drugs but it has had no discernable impact on rates of access to medicines, which almost certainly remain extremely low. Again, the fact is that there are far more serious problems at play which affect access to medicines besides intellectual property rights, such as an entirely inadequate medical infrastructure.

Nevertheless, the recent changes in India's intellectual property law already have stimulated Indian firms to develop drugs for diseases that predominantly affect the local population. For instance, Nicholas Piramal has recently opened a US $20 million research and development centre in Bombay to carry out basic research in a wide range of health problems, ranging from cancer to malaria. Ranbaxy (India's largest pharmaceutical company) and Dr. Reddy's are also pursuing similar R&D projects. India currently has the largest number of FDA approved pharmaceutical manufacturing companies outside the US, and has increased spending on R&D from 4 percent, five years ago, to 8 percent today.[20]

The change in patent law is also attracting significant foreign investment. Multi-national pharmaceutical companies such as Merck and Bristol-Meyers Squibb now see India as a prime location for establishing research facilities. India is attractive not only because of its lower basic costs, but also because of the many well-educated researchers that can reliably conduct capital-intensive clinical trials and more complicated forms of later stage drug development. The management consultants McKinsey estimate that by 2010, US and European pharmaceutical companies will spend US $1.5 billion annually in India on clinical trials alone (Padma, 2005).

Case study **Brazil's healthcare problem: Systemic failure falsely blamed on intellectual property protection**

Margaret Tse, Instituto Liberdade

Although Brazil's AIDS problem is often at the forefront of the consciousness of the global health community, in reality it is only a small part of the wider health crisis facing the region. Brazil's wider health problems must be seen in the context of the poverty and mismanagement that besets the country – an estimated one in four people in its total population (40 million people) live on less than US $2 a day (UNHDR, 2005).

Overcrowded and poor living conditions make those living in poverty especially vulnerable to communicable diseases such as tuberculosis and cholera. When people have limited access to health care and medicines, otherwise treatable conditions such as malaria and tuberculosis become fatal for the poor. Poor nutrition and compromised immune systems are also key risk factors for several major killers including lower respiratory infections, tuberculosis and measles. Fuelled by growing antibiotic resistance, inappropriate prescription of ineffective drugs, and poor adherence to medication, infectious diseases once believed to be under control have re-emerged as major regional threats.

Despite the apparent success of Brazil's HIV plan, the government is failing to properly utilise the treatments and drugs it already has at its disposal. Too often, imported drugs simply do not reach the patients who need them. For example, a June 2005 survey of government-supplied drugs showed that a large quantity of medicines purchased from foreign manufacturers expired without even leaving the warehouses. Closer inspection revealed four of the batches of medicines had sell-by dates from before 1999. An incredible 59 out of the 69 lots of medicines held by the Ministry of Health expired between 2003 and 2005. This astonishing waste is a symptom of the inefficiency of the government health sector which, like other areas of the Brazilian economy, is beset by corruption and vested interests.

The government has sought to shift the blame for the appalling rates of access to medicines onto foreign pharmaceutical companies, accusing them of overpricing their medicines and threatening to impose compulsory licenses. This appears to be an attempt by the government to cover up its own failure to reform the healthcare system. But in so doing it undermines the incentives that drive knowledge-intensive pharmaceutical companies, by subjecting research into AIDS drugs to huge political risk.

Deflecting domestic criticism onto foreign companies (and therefore their shareholders) is a short-term fix for a problem that requires a long-term strategy, especially given the mounting resistance to current treatments and the lack of improved therapies on the market.

The reality is that the costs of ARV treatment constitute only a fraction of the total cost of caring for those with HIV/AIDS. If treatment is dispensed without proper monitoring and care, this increases the possibility of non-compliance, which then increases the opportunity for resistance to develop. Instead, good health care demands a strict routine of proper nutrition and frequent visits to good clinics with highly-trained staff. The actual price of the medicine is a small proportion of the overall cost of a properly-managed health scheme.

Brazil's current AIDS problem is also the result of the failure of successive governments to address the issue while it was still in its infancy. The spread of HIV/AIDS has been a serious issue in Brazil since the end of the 1980s, but has been dodged by the political establishment for years as taboo. Had it been tackled head-on in the early days, we might not have more than more than 160,000 HIV positive patients needing expensive and complicated antiretroviral treatment today.

Estimates suggest that prevention would have cost about two percent of the cost of treatment. But instead of supporting public awareness campaigns, providing consultation clinics, training doctors, distributing materials to promote safe sexual behaviour and educating the public at large about the risks associated with the disease, the government ignored its responsibilities. Given that even the best therapies cannot cure the disease but only slow down the symptoms, the past failure to invest proper resources into prevention programmes is now being paid for in human lives.

Conditions in many middle-income countries are ripe for the establishment of viable pharmaceutical R&D industries that would significantly accelerate the process of inventing new treatments for the diseases of poverty. Countries such as Argentina, Brazil, China, South Africa, and Thailand have skilled workforces and world class research institutes. They also have extensive experience in the manufacture of high quality modern drugs, vaccines, and active ingredients, as well as the synthesis of new compounds and the conduct of downstream clinical trials (Yuthavong, 2001). Furthermore, they benefit from lower manpower and infrastructure costs as well as less costly maintenance for equipment and less costly raw materials.[21]

These countries could therefore exploit their competitive advantage in order to develop a researched-based pharmaceutical sector that could produce new drugs at far lower costs than the established western drug companies. This would improve access to medicines, as well as increase the pipeline of new medicines for the diseases of poverty. However, most of these countries have been held back by weak intellectual property laws that have favoured the development of copy industries rather than research-based industries.

Instead, the Brazilian government's threats to issue compulsory licenses are likely to undermine investments in R&D for HIV medicines – even if they have reduced prices in the short-term. The fact is that if a certain class of medicines carries this level of political risk, companies will shun the research, and instead view it as a kind of peripheral corporate social responsibility activity. Ensuring that profits can be made is the best way to ensure that companies invest sufficient resources in researching and developing the next generation of drugs.

Many Western firms are also seeking to partner with local expertise. One recent example is collaboration between Danish-based Novo Nordisk and Dr. Reddy's to create a new treatment for diabetes. Japanese firms have also expressed interest in investing substantial sums into Indian R&D projects. Instead of imposing prohibitive barriers, as it once did, the Indian government actively has courted these foreign investments by providing incentives, such as a 10-year tax break to pharmaceutical companies that are involved in research and development.

Such developments mean that an Indian firm may well develop a vaccine for malaria or improve current tuberculosis therapies, resistance to which contributes to the deaths of over 1,000 people each day in India alone. Investments are even going into R&D for a vaccine for HIV/AIDS. Human trials are underway for the second preventative HIV vaccine candidate produced in India.[22]

In a relatively short time, India's new patent law is also hastening collaboration between the information technology sector and the pharmaceutical and biotechnology industries. Until recently, the fledgling research-based biotech and pharmaceutical sectors relied on patenting in the U.S and Europe.

Instead of exporting raw materials and basic active ingredients that are used to manufacture generics, firms in India now have the ability to compete globally, producing high value-added, life-saving medicines. This will also contribute to the country's continuing economic growth and its concomitant increase in life expectancy (which has already risen from 36 years in 1951 to its current estimated level of 61 years.

Singapore likewise illustrates the benefits of improved patent protection. In 2001 it implemented a new patent law which brought the country into compliance with international standards. As a result, US $5 billion in FDI has helped to sustain that country's position as one of Asia's strongest economies. Singapore's burgeoning biomedical science sector has played a central role: output in 2004 was US $9.7 billion, a 33.2 percent increase on the previous year.[23] This is not limited to investment on the part of established western

Hypothetical: Creating a market for malaria treatment

To evaluate the impact of improved IP protection on incentives to develop and market a new drug for one of the diseases of poverty, consider the potential market for a new malaria treatment.

While the costs of researching and developing a new drug in the US and other wealthy countries are estimated to be US $800 million, the costs of developing a drug in a less developed country would be far lower. Because of comparative advantages of producing in those countries, we assume that the cost would be around US $100 million (taking into account failure rates, etc.).

Currently, approximately 300 million people suffer from malaria each year. If 10 percent of those pay for a new treatment, that amounts to 30 million treatments per year. Although patents are valid for 20 years after filing, the effective life of a patent for a new drug is on average cut to about 10 years because of the time it takes to develop, test and comply with regulatory requirements (IFPMA, 2004). That means a total of 300 million courses of treatment while the drug is under patent.

Assuming a discount rate of 15 percent, each course of therapy needs to yield a margin of only 62 cents in order for the developer to break even on sales. The average cost of production for a course of Artemisinin Combination Therapy treatment is currently estimated at US $2.40.[24] Assuming that a new drug would cost a similar amount, the total cost of one course of treatment need be only around US $3.50 for the developer of the drug to cover the cost of development, production and marketing – and even make a profit (albeit a relatively small amount). At such a price, a new, patented malaria therapy would be competitive in the market and might plausibly sell the necessary 30 million courses per year.

If it were possible effectively to patent a new malaria drug in relevant markets, it seems plausible that there would exist a private sector company which could produce a cost-effective and efficacious new malaria treatment.

Sadly, however, the barriers to innovation and access described in this report mean that the discovery and development of drugs for the diseases of poverty is currently not financially viable for private sector firms, except as part of their philanthropic efforts.

Drug patents are part of the cure

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Access to medicines is a serious problem in developing countries. Yet a global campaign that places all the blame on intellectual property rights reflects growing confusion and ignorance about this complex issue.

While patents may not provide a sufficient incentive to stimulate some forms of basic research, weakening intellectual property rights will reduce the level of investment in applied research and development, not increase it. The idea that intellectual property rights restrict access to technologies such as pharmaceuticals is predicated on a misunderstanding of the role they play in promoting development and prosperity overall. If people in the poorest nations do not have access to medicines, it has nothing to do with the presumed dark side of intellectual property trying to keep them poor. It is because they have failed to climb aboard the train of economic development.

The key to economic development is the presence of the institutions of a free society: property rights, the rule of law, free markets and limited government. Explosive rates of innovation have taken place in countries, such as South Korea, Mexico, Jordan and Singapore, which have understood that growth and prosperity can only occur once the institutional framework is in place.

Strong intellectual property rights, administered and enforced in an impartial manner, have been an important part of this framework. As a result, these countries have experienced the growth of 'knowledge-based' industries — to the benefit of all.

If intellectual property rights were responsible for restricted access to medicines in poor countries, then drugs should be plentiful in countries where the patents are expired or were never present. On the contrary, many critical drugs that remain absent from the shelves of Africa's pharmacies have been off-patent for 30 or 40 years. These include most anti-diarrhoea drugs, antibiotics, derivatives of penicillin and cephalosporin, many antihypertensive drugs and almost all antipyretic drugs.

Some advocate as an alternative to IPRs, 'open source' models such as the human genome project. But this project hardly serves as a basis for completely altering the current model based on intellectual property rights. While it has provided information with potential use, the benefits of its initial research must not be overstated. Removing property rights and making companies conduct open-source research and development could to lead to disaster. Without the chance of recovering investments, why would research-based pharmaceutical companies invest large sums in drug development?

Open-source models might work in some businesses that are not so capital-intensive, but it is a pipe-dream to rely on the philanthropy of chemists, physicians, researchers and financiers to contribute voluntarily to such schemes.

Without massive capital there will be no new research. Without new research, such evolving diseases as AIDS, tuberculosis, influenza and malaria will become unstoppable.

Instead of attacking intellectual property, friends of the poor should direct their efforts to promoting property rights (including intellectual property), the rule of law and the freedom to trade unfettered by arbitrary government interference in less-developed countries. These institutions do not just improve people's ability to buy drugs — they also affect nutrition, education, distribution, infrastructure, the wages of health staff and opportunities to set up businesses such as wholesalers and pharmacies.

Without the institutions of the free society, there can be no growth and no sustained improvement in the health of people who currently die from curable diseases. Intellectual property is not part of the problem; it is part of the solution.

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pharmaceutical companies, as a host of younger indigenous R&D companies are also scaling up their operations.[25] Singapore's emergence as a significant location for value-added R&D has also contributed to the search for new medicines for diseases endemic to poor countries. A high profile investment in Singapore is the Novartis Institute for Tropical Diseases, which opened in July 2004. It will focus initially on researching treatments for dengue fever and drug resistant tuberculosis.

Inappropriate levels of intellectual property protection in developed countries

From the above, it is clear that intellectual property protection in most lower-income countries is almost certainly too weak, with the result that the level of for-profit development of medicines for the diseases endemic to those countries is too low.

However, concerns have been raised that in certain respects, intellectual property protection in some wealthier countries may be too strong. In particular, we are concerned that in some cases patents are granted for what appear to be mere discoveries rather than genuine innovations. For example, in some cases a genetic sequence has been patented even though the use of that sequence has not been identified. This might have the perverse effect of creating too broad a patent, blocking downstream innovations. On the other hand, it is possible that without such patents, investments in biotech research would be far lower, and the discoveries that form the basis of downstream pharmaceutical products would never come into being.

Likewise, there has been much criticism of patents granted for research tools. These, it is argued, raise the cost of research without providing any substantive benefits. On the other hand, it is again possible that without the possibility of patents, there would be insufficient incentives to invest in the development of the research tool in the first place.

After the fact, it is often easy to argue that an invention was 'obvious'. To engineers who develop laser-guidance systems, the light bulb no doubt seems 'obvious'. To the developers of modern hybrid cars, perhaps the internal combustion engine seems 'obvious'. But the reason the innovations seem obvious after the fact is that they are already there and in some sense have been factored into all downstream innovations. What is not clear is whether they – and the downstream innovations upon which they depend – would in fact have been developed had there been no means by which the inventors could have captured the rewards of their investments.

Nevertheless, the question remains as to how best to ensure that patents that are granted are not too broad. This may be addressed in various ways. Some, for example, argue that greater pre-grant scrutiny of patents would reduce the number of egregious patents that are granted. In our opinion this is not a good solution. In a TRIPS-compliant system where patents are granted for 20 years after filing, it would likely further delay the granting of patents. This would both delay investments in R&D related to the patented innovation and reduce the effective life of the patent once granted. In the context of medicines, this would mean fewer new drugs and longer delays in their appearance on the market.

Others argue that the rules applied by patent examiners should be changed. For example, it has been suggested that patent applications should be evaluated not only on the basis of the three standard criteria (novelty, non-obviousness, and utility)[26] but also on the basis of their effectiveness. This, however, presupposes that effectiveness can be measured prior to the development and testing of a product, which usually it cannot – especially in the case of new molecular entities. In such circumstances, the requirement of 'effectiveness' will lead to arbitrary decisions by patent examiners and judges, and patents will not be granted to many potentially effective products.

We believe that there are better solutions, including:

- **Simplified procedures for granting patents.** At present, many countries have highly bureaucratised patent agencies, which are extremely slow in making decisions on the granting of patents; streamlining

procedures along the lines of international best-practice could improve the situation.

- **The introduction of regional patent granting agencies.** Where resource constraints are a problem for patent offices, such agencies could reduce costs and increase throughput, thereby increasing the competitiveness of the whole region.
- **Improved incentives for patent agents to make decisions.** For example, introducing a performance related pay system (appropriately constrained by quality requirements) might increase throughput of patent applications; contracting out the service to the private sector could have a similar effect.
- **Simplified procedures for challenging patents in courts.** This would enable more rapid and less costly resolution of disputes.
- **The introduction of petty patents or 'utility models'.** This would be useful for certain classes of product where a full patent might not be justified – these might apply, for example, to research tools and certain genetic sequences.
- **Competition between patenting authorities.** While it may be desirable to have common minimum standards for patents, such as those to which members of the WTO have agreed under TRIPS, it is important also to retain a degree of competition between authorities in order to ensure that the appropriate breadth of patents may be discovered.[27]

However this problem is addressed, it is important to remember that its effect is relatively marginal compared to the huge benefits of the intellectual property system and should not be a focus of the WHO. A more appropriate forum for such discussions would be the World Intellectual Property Organization (WIPO), which in fact already has such fora.

Pre-market regulations

Companies are required to comply with an increasing number of regulations before they can launch a pharmaceutical product onto the market. This drives up the costs of supply, making the end product more expensive and thus less affordable for customers in lower-income countries. According to a survey of 20 leading pharmaceutical companies conducted by the CMR Institute for Regulatory Science in 2003, 65 percent of companies felt that the change in the regulatory environment over the preceding three years had increased the cost and time of bringing new medicines to market. Furthermore, 23 percent of those surveyed felt that the increasing regulatory burden was directly responsible for the decline in NME submissions (CMR, 2004). In South Africa, the situation is exacerbated by the Department of Health's stipulation that it approve all new drugs, even if they have been approved already in the EU, US or Japan. This can add delays of two or more years before new medicines are available in South Africa.

Because regulatory bodies are beholden to national governments, their tendency is to ensure that the potential side effects of new drugs are minimised as far as possible. This is because the publicity surrounding the discovery of an unsafe drug in the market leads to a public outcry, resulting in high political costs for national regulatory authorities. The missed gains from new medicines that are delayed or refused approval are less obvious (or even intangible) to the general public, so regulators have an incentive to err on the side of caution. However, if the regulator only considers potentially harmful side effects, this will have the unintended consequence of raising the cost, and delaying or preventing the approval of new drugs.

One consequence of an excessively precautionary approach is that regulatory authorities allow new medicines or vaccines to be sold to the public only after extensive pre-clinical and clinical trials have been performed. These trials examine the safety, quality and efficacy of the new drug in treating or curing diseases. Estimates of the average time it takes to for a new drug to go through these trials range from 8.5 to 13.5 years, a process which adds considerable costs to the drug development process (DiMasi, 1995; Adams & Brantner, 2003; Dranover & Meltzer, 1994).

Estimates of the cost of bringing a new drug to market vary; some researchers suggest that the total cost is over US $800 million (DiMasi et al., 2003). As such, manufacturers have strong incentives to concentrate their

resources on developing 'blockbuster' drugs that will provide a return on that significant investment. Meanwhile, there is less incentive to invest in drugs for rarer conditions in the richer world (such as psychiatric disorders) and even for relatively common diseases in lower-income countries.

Professor Sir Michael Rawlins, Chairman of the UK's National Institute for Health and Clinical Excellence, has argued that many of the preclinical and clinical studies required by various regulatory agencies add little to the safety of the final product, but instead contribute unnecessarily to the estimated US $300–450 million cost of clinical development (Rawlins, 2004). Clearly removing excessively precautionary regulatory barriers would speed up drug development and reduce costs, creating stronger incentives to invest in the development of new drugs for diseases that may otherwise be relatively unprofitable.

To some extent, the length of time it takes for new drugs to enter the market, and the consequent cost to society of delays, is an issue recognised by regulatory agencies. The FDA has adopted 'fast-track approval' and 'accelerated approval' for certain classes of drugs, while the European Medicines Agency has instituted stiff targets for the marketing approval of orphan drugs. These represent a step in the right direction, but governments are often tempted to impose further regulations on drugs manufacturers when they come under political pressure. A recent example comes from the United Kingdom, where the health minister Lord Warner revealed that he is considering a fourth stage of clinical trials to alleviate safety fears surrounding new drugs. Legislators should resist the temptation to assuage public fears through such excessive regulation, because it would increase the time and expense of getting a drug to market. This would be most harmful for the development of drugs for regions or diseases where returns are the lowest – most typically, diseases endemic to lower-income countries.

One solution which would ensure that new drugs reach markets as quickly as possible — in part by reducing the ability of local drug regulatory agencies to impose arbitrary and overly stringent requirements on new registrations — would be to enable competition between existing national drug regulators, as well as between private certification boards (Sauer & Sauer, 2005).

Such accountable, competitive regulators would set the standards of regulation at levels demanded by those making choices about drug regimens. For many drugs, this would mean swifter approvals and a reduction in development costs, leading to an increase in the number of drugs developed for most diseases – especially those which affect the poorest and those which affect relatively smaller populations – while also reducing the price of medicines to all.

Public health would be safeguarded by the desire of these agencies to defend their own reputations. The importance of reputation in maintaining clients and attracting new ones, the existence of a free press engaging in investigative journalism, and expected penalties through the legal system for corrupt and dangerous decisions by these regulators, should lead to a well-functioning market in drug approval. A drug approval agency that bends to pressure from pharmaceutical companies, for example, would be quickly exposed, and the marketability of their future products would suffer.

Data exclusivity

Another aspect of pre-market regulation is the treatment of the data submitted to regulatory authorities. These data are submitted on the basis of 'data exclusivity', an agreement that the authorities will not release them for a specified period and that during this period other firms may not rely upon the data as the basis for their applications for licenses.

This period of data exclusivity varies from 5 to 11 years.[28] Once it expires, competing companies are free to access and rely upon the data and thereby avoid having to conduct duplicative research (and associated costs).[29]

It has been alleged that these periods of data exclusivity hinder generic competition, thereby keeping the price of medicines unnecessarily high. But while the introduction of competition typically leads to price reductions on

medicines, the net effect will depend on the impact it has on the incentives to invest in research and development. Companies invest heavily in the development of the data they supply to regulators during the approval process. If these data are then shared with other companies, the value to the originator is reduced. This erosion of value has negative consequences for the ability to raise the funds required to conduct future tests, and is likely to act as a disincentive to companies which might otherwise bring new, therapeutically beneficial medicines to the marketplace.[30]

Unclear rules governing the submission of data to regulatory authorities will only increase legal disputes between research-based companies and their generic counterparts. These disputes are already common and their frivolous costs must now be factored into the rapidly rising total cost of delivering a drug to the marketplace. While great effort is being expended towards containing these costs, the failure properly to address data exclusivity arrangements threatens not only to increase costs, but also to reduce the incentives to innovate as well.

Price differentiation

The ability to sell a product at different prices to different consumers enables companies with a degree of market exclusivity to ensure that their products reach as many consumers as possible while still maximising revenue. If a company is able to segment markets precisely according to each individual's willingness to pay, then every consumer willing to pay at least the marginal cost of production for the product should be able to purchase that product. This would both maximise the number of people who benefit from the product and would also maximise revenue to the company, which in principle would enable more to be spent on R&D.

Perfect market segmentation means that the number of consumers served and the price paid by the poorest consumer are the same as that which would exist in a perfectly competitive market (Appendix Figure 5).

In practice, market segmentation is costly to enact – primarily because of the need to prevent low-price purchasers reselling to higher-price purchasers – and the larger the number of market segments, the greater the cost. So, firms weigh up the benefits of adding a segment with the cost of enforcing the additional segmentation. Typically, firms segment markets first by overall market (which is usually a country or trading bloc) and then by sub-categories, such as: individuals (which may be further segmented by age and income), businesses, charities, and governmental bodies. So, for example, drug prices in South Africa are far lower than in Europe and the US (Reekie, 1997). This means that market segmentation can be particularly beneficial for patients in poorer countries.

Where the overall market for a product is very large and where that market is readily segmented (i.e. the cost of enforcing the segmentation is low compared to the benefits), companies may set the lowest price close to the marginal cost of production. In the context of a disease such as HIV/AIDS, where the total market for medicines is massive and the humanitarian case for widespread distribution is great, companies may even choose to sell below marginal costs in some markets, provided that sufficient profit is recuperated in others (Danzon & Furukawa, 2003).

Market segmentation is underpinned by intellectual property – especially patents and trademarks – and contracts. If the intellectual property rights and contracts are respected,[31] firms can operate freely within the marketplace without running the risk of having separate national or international markets compromised by the resale of the lowest priced medicines into markets where prices are relatively higher.[32] However, infringements upon intellectual property rights mean that firms cannot control their own pricing schemes, with serious consequences. Not only does this act as a disincentive for firms to sell their products in poor countries, it may also inhibit future innovation.

In short, price differentiation allows companies to cater for people who otherwise could not afford to purchase their products. It allows countries that are not able to shoulder the costs of R&D themselves to afford expensive medicines. It also means output is higher than the level that would occur if no differentiation were

possible. Moreover, the innovator is able to generate more revenue, providing a greater pool of resources for investing in new drug development.

Price controls

Unfortunately, governments often restrict the ability of companies to implement differential pricing strategies. For example, they frequently impose price controls on drugs, capping the price of drugs and making any other sales price illegal. Nearly all economically advanced countries – with the notable exception of the United States – impose price controls on medicines in one form or another (Danzon & Furukawa, 2003). Because the controlled price is effectively the *only* price, this prevents competition that would drive the price lower; in other words, the price 'ceiling' becoming a price floor (U.S. Department of Commerce, 2004).

Drug price controls discourage companies from registering products in certain markets, leading to shortages in supplies and illegal trade in medicines. This in turn provides a route for counterfeit medicines to enter the market. A 2003 study illustrated that one of the risks of parallel importation from countries which have regulations that ensure low drug prices is that medicine manufacturers prefer to delay or cancel the launch of a particular product in the price-controlling countries (Danzon et al., 2003). The study showed that between 1994 and 1998, there were 85 New Chemical Entities launched in the US and UK. However, out of a maximum possible 2,125 registrations of these NCEs in 25 countries, only 55 percent (1,167) were actually registered. The research also showed that those countries with lower expected prices or a smaller expected market size – most typically lower-income countries – experience longer delays in drug registration.

Delays in registration of new medicines are particularly harmful to sufferers of HIV/AIDS. Research shows that one new anti-retroviral (ARV) HIV/AIDS drug prevents around 6,000 deaths in the US the following year and ultimately prevents around 34,000 deaths (Lichtenberg, 2003). Although new ARVs cost more than older, off-patent ones, they can substantially reduce the number of lost productive work days, so in many cases pay for themselves in a purely financial sense (one study estimated that 21.3 percent fewer days were lost with the introduction of each new ARV) (Lichtenberg, 2003). Newer drugs also reduce the amount of time patients spend in hospital, negating any financial benefit from using older, off-patent drugs.

Price controls also have a number of other adverse impacts:

Reduced supply

Regulations on drug prices drive pharmacies into bankruptcy as their margins are squeezed, and make the distribution of drugs to remote and rural regions financially unviable. For example, the price caps forced on certain drugs in South Africa have been implicated in the closure of 103 pharmacies.[33] Price controls will likely reduce profit margins on controlled-price pharmaceuticals. As a result, wholesalers and pharmacies are likely to carry a smaller range of drugs. If the price controls are widespread or targeted at the most popular drugs, they may have such a negative impact on profits that it is not worth a wholesaler distributing them to far-flung pharmacies – and so pharmacies in rural areas will be more likely to close. The lack of profitability in the sale and distribution of medicines will also reduce the incentives for pharmacists to invest in training, which will make them less effective purveyors of healthcare advice. This would be particularly damaging to the rural poor, whose contact with professional healthcare is very often limited to local pharmacists.

Reduced innovation

In many countries (especially Canada, and countries in Europe and Australasia), government control over healthcare systems has led directly to price controls of one kind or another. Ageing populations, combined with more effective but more costly treatments for many diseases puts upwards pressure on healthcare costs. Politicians may be wary to increase spending on health, especially where the spending affects the incomes of taxpayers and can be seen as the result of their actions – because of the potential it could have on their chances to be re-elected.

The relatively short electoral cycle creates incentives on the part of politicians to achieve short-term savings, even when these will lead to longer-term costs or longer-term harm to health. The result has been strong pressures to restrict access to more costly new pharmaceuticals which are relatively more expensive, even though in many cases these new drugs would reduce the subsequent need for more expensive procedures and hospital treatment.

A striking example comes from Canada, whose Patented Medicines Review Board sets strict guidelines on the price of medicines. This board also has the power to compel a supplier to reduce prices if they exceed pre-determined levels (Menon, 2001). Likewise, Germany's government sets levels at which it will reimburse purchases of specific classes of drugs, with consumers paying any difference. This has the result that the consumer's perception of the cost of buying newer drugs is much greater than the real price differential. As a result, consumers have an incentive to buy older drugs that are less effective.

Price controls reduce the ability of producers to implement effective price differentiation strategies. In essence, fewer drugs are supplied at a price higher than would be paid by the poorest consumer but lower than would be paid by the wealthiest consumer. As a result, wholesalers and retailers are likely to carry a smaller range of drugs. If the price controls are widespread and targeted at the most profitable drugs, they are likely to have a substantial impact on profits throughout the value chain. That means not only fewer wholesalers and pharmacies, but also less investment in new drugs by pharmaceutical companies. (The economic consequences can be seen in Appendix Figure 6.)

Economic theory is backed up by increasing amounts of empirical evidence. Price controls have had a direct negative impact on the numbers of new drugs that are submitted for regulatory approval. A recent US Department of Commerce study found that the price controls used by a range of OECD countries have resulted in a significant decrease in spending on both old and new drugs (U.S. Department of Commerce, 2004). It found that these controls have decreased the price, pushing it closer to marginal production costs, which in turn leaves less revenue for future investment in R&D. The study estimated that, after extrapolating to a broader set of OECD countries, the diminished returns as a result of price controls are in the range of US $18 billion to $27 billion annually. If this lost revenue could be recouped through deregulated pricing strategies, the study calculates that an additional three or four new molecular entities (NMEs) could be developed every year. To put this into context, only 30 NMEs were approved by the FDA between 2000 and 2003.

Price controls in some European countries have also hindered Europe's ability to develop new medicines. In 1992, six out of ten best selling medicines were developed in Europe; by 2002 only 2 out of 10 were of European origin. If the US were to introduce price controls, it is estimated that this would result in a reduction pharmaceutical R&D by some 30 percent. This would translate into 330 to 365 fewer new drugs within a twenty-year period (Giacotto, 2004).

Compulsory licenses

Compulsory licenses – or the threat of issuing a compulsory license – can have a similar effect on innovation as price controls. In the interest of improving public health, compulsory licenses can be a way for extremely poor countries to procure relatively inexpensive medicines (when all attempts to secure such products voluntarily have been exhausted). The issuance of such licenses in a medical state of emergency has always been permitted under the original TRIPs Agreement for countries with manufacturing capacity. The 2001 WTO Doha TRIPS agreement extends this safeguard to countries without manufacturing capacity – enabling them to procure from companies with manufacturing capacity but where otherwise production would be restricted to patent holders – thereby protecting the interests of the poorest nations.

In practise, however, middle-income countries such as Brazil have often used the threat of compulsory licensing as a negotiating tool to secure lower prices.[34] While this can prove to be a politically popular move in the short term, it undermines the ability of innovator companies

effectively to price differentiate. It also places increased strain on pricing strategies aimed at offering the cheapest medicines to patients in extremely poor countries, and acts as a further disincentive for firms to develop new and improved medicines for the diseases of poverty (Kremer & Glennerster, 2004). (Appendix Figure 4 shows what would happen if both demand and supply-side constraints were lifted.)

Discussion

Clearly, many urgent health concerns in the poorest parts of the world could be addressed if existing drugs and interventions were to be distributed properly. However, a variety of factors conspire to prevent people from receiving the medicines they need. As we have seen, poor road and electricity networks hinder the distribution of drugs, as does the shortage of medical facilities such as clinics, hospitals and pharmacies. Health insurance systems, which would enhance access to medical care, are currently inadequate because the governments of lower-income countries frequently fail to foster the kind of institutional environments in which they can thrive.

But people are also denied medicines in more insidious ways. Governments in lower-income countries impose burdensome taxes and tariffs on imported medicines, pricing many people out of treatment. Governments also impose often unjustifiable non-tariff barriers, such as arbitrary licensing restrictions. At the same time, governments nominally offer healthcare services to everyone, but in practice they do so in ways that primarily benefit a small number of citizens (mostly the elite) at a very high cost. As a result, government-financed healthcare systems in such countries are often poorly resourced and poorly managed. Meanwhile, the private sector often is over-regulated. These glaring failures of governance help to ensure that universal access to essential medicines remains a long way off for many regions of the world.

The manifold failures in drug distribution also have ramifications that reach beyond the immediate health needs. Because these failures diminish demand for medicines, they make it less likely that new medicines will be created. In richer countries this is less of a problem because effective demand is higher.

Producers respond to the perceived demands of consumers, whether those consumers are individuals, health agencies, insurance companies or governments. (This is illustrated in Appendix Figure 1.) This has led to the creation of a wide variety of drugs to combat the range of disorders suffered by consumers in rich country markets. However, in lower income countries the absolute size of the market is constrained by the weakness of distribution mechanisms, leading to a concomitant decrease in supply. If a medicine stands little chance of actually reaching its intended consumer, there is little point in risking large amounts of capital in developing a drug specifically designed for a poorer market. As a result, certain diseases endemic to these regions, such as the cluster of so-called 'neglected diseases',[35] have failed to attract sufficient research from commercial drugs companies. In the next chapter, we consider some possible mechanisms by which this problem may be overcome.

4

Incentivising R&D for the diseases of poverty

Despite ongoing problems with delivering medicines in resource-poor settings, there remains a need for new, innovative treatments. Bacterial and viral resistance to existing treatments is a major problem in treatments for diseases such as malaria, tuberculosis and HIV/AIDS (Zumla & Grange, 2001; Ridley, 2002), while some researchers have expressed dissatisfaction with current R&D and existing treatments for tuberculosis (Moran et al., 2005). Constant efforts must be made to ensure the development of new treatments for these diseases. In addition, specific subpopulations such as pregnant women and children are most at risk from diseases such as malaria, and require medicines with specific formulations (Bremen, 2001). Furthermore, some diseases lack any effective and safe treatments; in particular this applies to African Trypanosomiasis, leishmaniasis, Chagas disease and Dengue fever (WHO/IFPMA, 2001).

Incentivising R&D for dysfunctional markets

The lack of effective distribution of existing medicines in many poor countries, combined with the low purchasing power of potential consumers, means that the market for new medicines for the diseases of poverty is currently weak. If the problem of distribution was overcome, the size of the market would increase, even if purchasing power remained low. In principle this should stimulate innovation, as companies seek to fulfil unmet wants.

However, the relatively small size of the market is not the only barrier to the creation of new treatments for the diseases of poverty. As we have seen, governments in poor countries exacerbate the weaknesses of the existing market through a host of short-sighted public policies. These include (but are not limited to) the imposition of taxes and price controls on essential medicines, weak intellectual property laws and generally poor law enforcement.

Win-win solutions

The issue is how to create incentives for the development of new drugs to treat and prevent the diseases of poverty without diverting scarce resources from distribution. On the basis of the evidence presented in Chapter 2, we are concerned that many more lives might be saved if scarce public resources were utilised to improve healthcare delivery systems in lower-income countries, rather than using those same resources to develop new drugs. Nevertheless, there is certainly a need for new treatments and drugs that address diseases and challenges which are unique to these countries.

In order to square this circle, we need to create win-win solutions that will incentivise the development of new medicines, while at the same time not drawing limited funds away from the distribution of medicines and other healthcare priorities.

Most new medicines – including over 90 percent of those presently on the WHO's list of 'Essential Medicines' – were developed by the private sector (Europe Economics, 2003). Given that, it is important to understand what motivates the private sector to develop a new drug, and how this is affected by various political and economic factors.

Mechanisms for funding R&D

In the short term, it is unlikely that policymakers in low income countries will improve the institutional environment sufficiently to rectify the glaring gaps in both the demand for and supply of new medicines to treat the diseases of poverty. In the absence of a properly functioning market, other ways to encourage the development of new medicines must be found.

Any mechanism designed to encourage the development of new medicines for the diseases of poverty must – to a greater or lesser degree – overcome the various regulatory and cost barriers discussed in other sections of this report, as well as ensuring that a useful product eventually will be produced.

Generally, such mechanisms can be split into two categories: 'push' and 'pull.' Push mechanisms enhance the funds available to research and development, in the hope that a useful drug will be produced; pull mechanisms provide enhanced incentives for investments in R&D by increasing the value of the end product to the innovator. Reducing the burden of taxation on R&D investments made by private corporations is one example of a 'push' mechanism for targeted research projects. [36] An example of a pull mechanism is the offer of a reward to the inventor of a drug that treats a specified disease. We discuss specific push and pull mechanisms in more detail below.

Push mechanisms

Push mechanisms aim to encourage the development of treatments for specific diseases by providing upfront financial support for research into those diseases.

There are, however, significant drawbacks to upfront funding. Subsidies to R&D do not necessarily lead to the development of useful medicines. Estimates suggest that of every 5,000 new chemical entities (NCEs) screened, on average only five go through to clinical trials, and only one of those yields an approved medicine for patient use (ABPI, 2002). Publicly-funded projects that focus on the development of only a few selected chemical compounds are therefore quite likely to fail, resulting in the waste of significant sums of public money.

There are two main types of 'push' mechanisms: direct funding and public-private partnerships.

Direct funding

Direct public funding might take the form either of public funding for research and clinical trials carried out by private firms, of increased funds to public, non-profit research organisations or a combination of the two. [37]

Advocates of direct funding argue that subsidised or even wholly nationalised research and development is the best way to produce safe and effective medicines for the diseases of poverty (Hubbard & Love, 2004).

Notwithstanding the previously addressed issue of distribution, the problem with direct funding is determining exactly what level of financial resources are required to develop a successful treatment, and how best to deploy those resources to create an incentive-compatible system.

First, it is extremely difficult to determine at the outset the exact amount of funding that will be required. Second, there is also a risk of overspend as the project may encounter previously unknown obstacles or avenues of research. Third, project leaders may be tempted to exaggerate the likely cost of research in order to secure as much funding as possible.

Finally, the involvement of public stakeholders may skew research objectives, as their demands may reflect political rather than clinical preferences. This is particularly evident in the case of AIDS, a disease that attracts significant political attention. This increases the likelihood that research into AIDS would be over-funded, at the expense of other, less headline-grabbing diseases like diarrhoea and respiratory infections which merit equal or greater consideration (Craven, 2005).

In addition to inefficiency and waste, there is no guarantee that a government subsidy will produce any of the specified outcomes. A straightforward illustration of the drawbacks to public procurement of R&D was a US Agency for International Development (USAID) initiative in the 1980s to fund development of a vaccine for

USAID Funding for a Malaria Vaccine

Consider the example of US Agency for International Development (USAID) funding of research into a vaccine for malaria described eloquently by Rachel Glennerster and Michael Kremer (2000, pp. 37–38):

> "*USAID decided in the 1980s to finance three teams seeking a malaria vaccine. One team developed a candidate vaccine, but only two of nine volunteers tested were protected from malaria, and the tests indicated that the vaccine created side effects. Those results, mixed at best, did not prevent USAID from issuing wildly optimistic statements. In 1984, the agency claimed that there had been a major breakthrough in the development of a vaccine against the most deadly form of malaria in human beings. The vaccine should be ready for use around the world, especially in developing countries, within five years. Fifteen years later, the world is still waiting for a malaria vaccine*" (cited by Desowitz, 1991, p. 255)

Early work by a second team yielded disappointing results, but, not surprisingly, the principle investigator argued that his approach was still worth pursuing and requested an additional US $2.38 million from USAID. The expert consultants assigned to review the project recommended against funding the research, but James Erickson, USAID's malaria vaccine project director, told the USAID Office of Procurement that the expert panel "had endorsed the scientific methodology and the exceptional qualifications and experience of the researchers" (Desowitz, 1991, p. 258). Once the grant was awarded, the principle investigator transferred grant funds to his personal account. He was later indicted for theft.

Although outside evaluations of the third team's progress called it mediocre and unrealistic, Erickson arranged full funding for the project. The principle investigator and his administrative assistant later were indicted for theft and criminal conspiracy for diverting money from the grant to their personal accounts. Two months before the principle investigator's arrest, the Rockefeller Foundation gave him a US $750,000 research grant, and on that day the investigator was arrested, USAID announced it was giving him an additional US $1.65 million for research.

By 1986, USAID had spent more than US $60 million on its malaria vaccine efforts, with little to show for it. Nevertheless, because USAID believed that there would be many candidate malaria vaccines suitable for testing, it tried to obtain monkeys as test subjects for those vaccines. Erickson arranged for a contract to acquire monkeys to go to an associate who paid him a kickback. Erickson eventually pleaded guilty to accepting an illegal gratuity, filing false tax returns, and making false statements.

USAID had arranged for independent oversight of the project by the American Institute of Biological Science (AIBS). Erickson and the AIBS-assigned project manager were lovers.

Glennerster and Kremer conclude that:

> "*Although the USAID project is an extreme example of waste, fraud, and abuse, it illustrates some important points about government-funded research: First, recipients of government funding have incentives to be overly optimistic. Second, government funded project directors have incentives (aside from embezzlement opportunities) to fund unpromising research. Third, because the recipients of government subsidies are paid before delivery, they may be tempted to divert resources away from the search for a vaccine*" (p. 38).

Source: Morris et al., 2001

malaria. This initiative absorbed US $60 million but failed to achieve any of its goals (see box on page 48).

Underlying the problems with the USAID malaria vaccine initiative was that the researchers were operating to the demands of a public sector employer rather than the market. By now, a considerable literature has developed to explain the poor performance of the public sector. Essentially, it does not have the same incentives as commercial firms for efficient supply of goods and services (Tullock, 1965; Niskanen, 1971; Downs, 1967; Borcherding, 1977).

Commercial firms are highly responsive to the desires of their customers, for it is the customers who supply revenue to the firms. A government-run organisation is typically less responsive to the individuals it is servicing and more responsive to the legislators who support it through budgetary provisions.

Public private partnerships (PPPs)

Rapid advances in science and technology, especially the ever-increasing number of new biological and chemical discoveries, mean that even large firms are unable to follow all new developments in research. One example would be the expanding number of biological targets now available due to the expanding field of genomics. The cost of tracking all such developments is beyond the means of most individual firms. Research-based pharmaceutical companies rely increasingly on special relationships between small entrepreneurial firms that specialise in scientific research.

This process has also been supplemented by public private partnerships (PPP), which complement private drug development for specifically targeted diseases. One such example of this model is the National Institutes of Health (NIH), which operates in the United States. In 2003, the NIH provided more than US $27 billion to fund and coordinate health research, making it the largest public health research body in the world. The NIH national research centre supports research in many different fields and also coordinates activities by many researchers, including small scale biotechnology firms. These research projects provide inventories of promising chemical compounds which can be utilised by private sector research-based companies to develop medicines.

Several public-private partnerships exist that specifically focus on diseases of poverty. In particular, the Medicines for Malaria Venture (MMV), the Global TB Vaccine Foundation (Aeras),[38] the International Aids Vaccine Initiative (IAVI), and the Infectious Disease Research Institute (IDRI)[39] coordinate publicly-funded R&D projects with private companies. Due in part to these arrangements, there are at least 63 drugs in the R&D pipeline targeting HIV/AIDS, including 15 vaccines (Moran et al., 2005). There are at least 30 more drugs in the R&D pipeline for malaria, and 22 for tuberculosis.[40]

In addition, there are now PPPs that focus on developing drugs for African Trypanosomiasis, Chagas Disease, Leishmaniasis and Dengue Fever, which have bolstered the number of potential treatments in the R&D pipeline for diseases that disproportionately affect people in poor countries. There are currently at least eight potential treatments in varying stages of clinical trials, and a further 16 in preclinical development.[41]

Research at the London School of Economics shows that the PPP approach has outperformed stand-alone industry efforts in producing drugs that are particularly suited for conditions in less developed countries. PPPs have often proved to be a quicker way to get drugs to market, generally equalling or exceeding industry standards. Finally, it appears that PPPs are more cost-effective than other approaches. For example, the Medicine for Malaria Venture's synthetic peroxide project has moved to Phase I clinical trials for a total cost of US $11.5 million – lower than the industry norm for developing a New Chemical Entity for western markets (Moran et al., 2005).

Because the process of drug development takes many years, it vital to ensure that PPPs have sustainable and reliable sources of funding. For this reason, private (including philanthropic) funding may be preferable to government support, because it is not hostage to as many political factors. A government facing fiscal problems, for instance, might turn to its PPP funding commitments as a relatively invisible form of cost-cutting. PPPs that derive their finances predominantly from public sources may

also suffer many of the problems associated with direct funding, which have already been discussed. If too much reliance were to be placed on public funding for PPPs, it would attach an unhealthy level of risk to their long-term viability. Finally, if too much public funding were forthcoming, it has the potential to crowd out private providers.

Pull mechanisms

While push mechanisms require funding up front for research activities in the hope that they will develop a useful drug, pull mechanisms act at the other end, providing funding or other pecuniary incentives only when a specific, predetermined outcome has been achieved.

Pull mechanisms have the singular advantage for the funding entity that they receive payment only after a demonstrably effective and tested product has been manufactured. This means that drug developers can carry out drug development without interference from the funder, while the funder is liberated from the responsibility of having to manage the R&D process. Furthermore, because the funder only pays for the drug when it has been fully developed, the possibility of being left with a costly white elephant is dramatically reduced.

However pull mechanisms have several potential drawbacks (Kremer & Glennerster, 2004). First, the donor must specify the outputs before research commences, which may be difficult. Second, if outcomes are not well defined, it may not be clear what basic research is necessary, so the whole project could stall – indeed there could be serious consequences for the whole stratum of basic research, especially if the model were applied widely. Third, developers may – legitimately, given the fickle nature of political commitments – be concerned that the funder might renege on his commitment. Finally, because pull mechanisms often result in a 'winner takes all' situation, they run the risk of stifling the incremental innovation that results from 'inventing around' the original drug, which could have beneficial implications for future drug-resistance and effectiveness in subpopulations.

Some concerns have also been raised that offering publicly-underwritten, commercial incentives to drug companies to conduct such work could undermine much of the useful work that is currently being undertaken by the various PPPs and industry neglected-diseases institutes (Moran et al., 2005). This is because many of the multi-national pharmaceutical companies have opted to devote resources to this area for a range of reasons aside from direct commercial advantage. These include broad public relations considerations; corporate social responsibility; and strategic reasons such as gaining exposure to as yet untapped markets. This risk is that by dangling pecuniary carrots in front of such companies (for example in the form of Advance Purchase Commitments), governments could tempt companies to cease work on PPPs and instead switch to these other projects. This would be expensive, as currently the cost of R&D is borne largely by the companies themselves and does not entail any costs for taxpayers or government treasuries. The bill for a successful APC, on the other hand, will require billions of dollars of public money. Notwithstanding these criticisms, pull mechanisms offer considerable promise for the development of treatments for certain diseases. Some notable proposals are discussed below, with a brief evaluation of their strengths and weaknesses.

Transferable patent extensions

One suggestion has been to grant a patent extension for an existing product in a particular market to pharmaceutical R&D companies based in wealthy markets such as Europe, the USA and Japan. In return, the company would invent a vaccine or treatment for a disease of poverty on a pre-determined list. This mechanism would be attractive to larger, established R&D companies, and it would likely result in an additional flow of private sector resources into the quest for drugs for the diseases of poverty. Also and significantly, it does not rely on uncertain funding from governments.

If – as was originally proposed – the patent extension were to apply only to one product, the effect would be to transfer the financial burden of developing new medicines for the diseases of poverty onto consumers of

a few specific drugs in rich markets. This is ethically dubious, since it effectively forces a possibly small and relatively well-defined group of patients in rich countries to pay for the development of a completely unrelated drug for use in another country. Imagine if a government announced that it planned to impose a tax on the same group of people to pay for research on diseases faced by other people; this would unambiguously be a bad tax. Such a narrowly targeted patent extension might prove to be politically difficult, with affected patient groups lobbying against such extensions.

If companies were instead offered the possibility of extending the patent life on a range of their drugs for a shorter period, these objections would be substantially reduced. For example, instead of extending the patent on one drug by three years, pharmaceutical companies that develop a new drug for a neglected disease might in return be given a three month patent extension on a dozen drugs. This would disperse the cost over a wider range of consumers, making it both ethically and politically more acceptable.

Advance purchase commitments

Another potentially useful way to stimulate R&D into the diseases of poverty is for donor agencies or governments to guarantee in advance the bulk purchase of a drug that meets a set of pre-established criteria. The funder would make a legally binding commitment to pay for a new drug if and when one is developed, which would be set at a price sufficient to cover the cost of R&D.

According to the Centre for Global Development, a prominent supporter of such schemes, this would create a win-win solution for both donors and the private sector. For donors, such a commitment would have no impact on their existing budgets, and would not mean that funds are diverted to research projects which run a high risk of failure.[42] For drug developers, the main advantage lies in the fact that new markets would be opened in previously unattractive areas, while at the same time the risk of compulsory licensing would be removed. It would also reduce the chances of industry being compelled by any government to conduct research into unprofitable areas.

The main objection to such schemes lies in the problems associated with the valuation of the end products. The donor will not be able to assess the financial value of the final innovation in the same way consumers would, which may lead to under- or over-reward. Advanced purchase commitments also suffer from the so-called 'hold up problem.' Since the innovator's costs are already sunk, the prize-awarding body may be tempted to award prizes which are much lower than the true value of the innovation. Both of these factors will erode incentives for future innovation. Conversely, there is also the risk that R&D companies may be tempted to exaggerate costs in order to secure a greater reward from the funder.

Advance purchase commitments may also stifle incremental innovation. Because they create a 'winner takes all' solution, it would be difficult for incremental, follow-on competitors to emerge, thus dulling the benefits of competition on cost and improvements. The innovation that 'wins' the prize will crowd out competing inventions because it is being given away 'free' (i.e. at no cost to the end consumer) by the public sector. This will send the wrong signals to would-be developers of therapeutically useful medicines in the pipeline or waiting to enter it. This 'crowding out' effect means that no improvements are likely to be made to the 'winning' formulation, which poses serious problems once resistance develops in different subpopulations, rendering APC-rewarded medicines less effective and making the disease ultimately more difficult to treat.

As tends to be the case with publicly funded prize mechanisms, the potential for political rent-seeking is great, as the prize-awarding authority may be tempted to favour political or commercial allies. Lacking market mechanisms which might otherwise guide their decisions, senior individuals within the authority might have their incentives adjusted by inducements from companies eager to win the prize. Furthermore, the donor's view of what constitutes a socially useful innovation will reflect their own priorities, and could result in certain diseases or ailments being neglected or over-prioritised. Project choice, for example, might reflect the preferences of bureaucrats rather than those on the ground. Priority setting by outside agencies might result in R&D being

directed only at one type of country, one region of the world, or one disease – with other equally needy causes missing out on the additional investment.

It is also worth considering the historical record of prizes – of which advance purchase commitments are a special type – as a stimulus to investment. In individual instances, these have clearly worked in the past. For example, a prize from the British government led to the creation of the Harrison clock – though this was not without problems, including interference in the judging process from competitors (Sobel, 1996). More recently, the US $10 million, privately funded Ansari 'X Prize' most likely contributed to the development of the first major private sector spacecraft.[43] Yet it is doubtful that prizes can in general be relied upon to deliver new developments. In part this is because prizes require clear pre-specification of what is to be achieved – yet in many cases this is not possible: many innovations are unforeseen even by the researchers themselves. In part it is because those setting the prizes often do not know what level of reward is likely to be sufficient to remunerate investments in innovation. The experience of the Soviet Union is apposite: innovators in the USSR were rewarded for less than the value of their innovations and unsurprisingly the USSR's record of industrial and scientific innovation was not impressive.

If advance purchase commitments are to work successfully, they must be clearly targeted and the conditions – including both the conditions for success and the size of the award – clearly specified.

Orphan drug type legislation

While not related specifically to the diseases of poverty, orphan diseases share similar characteristics to those suffered predominantly in low-income countries. The relatively small numbers of people who suffer from orphan diseases make it unprofitable for private sector companies to make the investments that would be needed to develop specific drugs for them. In the United States, these include Huntington's disease, myoclonus, ALS (Lou Gehrig's disease), Tourette syndrome and muscular dystrophy.[44]

The US orphan drug legislation combines several interesting aspects of individual push and pull programmes to stimulate private sector R&D activities for the development of treatments for rare diseases. These include offering market exclusivity for 'orphan'[45] products receiving Food and Drug Administration (FDA) approval, tax credits for R&D investments,[46] and an orphan drug development grant program to provide funding for eligible researchers.[47] Most importantly, orphan drug applications are eligible for fast-track regulatory approval,[48] which makes the drug development process less onerous and less costly. These legal interpretations only make the option of pursuing R&D projects more interesting for private researchers, and therefore enhance the chances that new and improved medicines will be developed. While not identical, there is similar legislation in place to incentivise more private-sector research into rare diseases in Australian, Europe, Japan and Singapore.

Since the original US Orphan Drug Act was passed in 1983, more than 900 drugs and biological treatments have been designated as orphan products, and over 200 have been given FDA approval (Peabody et al., 1995).[49] Further reducing regulatory barriers for drug developers can stimulate more research on all disease, not just 'orphans'. Changes in legislation have yielded some beneficial innovations that otherwise might not have been introduced. These encouraging figures show that policymakers can respond to concerns about spiralling healthcare costs in ways that both encourage private sector companies and also bring down costs of new medicines for consumers.

However, with escalating costs of drug development caused in part by a lengthy and often tedious regulatory approval stage, policymakers should move to consider other options that expedite the development of new medicines for all diseases. One such measure would be to make regulatory agencies competitive amongst each other. This would induce them to be more responsive to market demands for the approval of high quality, efficacious and inexpensive medicines into the marketplace, free of the extra costs that accumulate as a result of overly bureaucratic, state-protected, regulatory agencies (Sauer & Sauer, 2005).

Open source

In addition to the 'push' and 'pull' mechanisms described above, it is worth discussing a recent proposal that drug development could occur to some extent in an 'open source' environment.[50] The concept of 'open source' is common in software development, and refers to a situation where developers share intellectual property with one another and develop new technologies collaboratively. In the context of software, several applications, including the Linux operating system, Apache server software, and the Firefox web browser[51] have emerged as moderately successful products, competing against more widely-known brands.

Open source has been suggested as a way to limit the costs incurred by any one individual or research agency during the lengthy process of drug development. It typically would rely on an electronic network of scientific researchers from a host of different organisations, including corporations and universities, who then work together for a common cause, in this case to research and select the most promising chemical compounds for a specific disease, and then eventually to develop treatments.

The major advantage of open source is that any decentralised research project can draw on scientific expertise from various participants without worrying about intellectual property issues. Given the currently low cost and remarkable ease of communicating over the internet, the possibilities for collaboration have expanded dramatically. A team of scientists working together instead of in direct competition may also reduce the chances of duplicative research, and may reduce the errors made during isolated research efforts, notwithstanding the indirect research results that these 'wasteful' efforts can bring.

In the context of drug development, open source could conceivably apply at various different levels in the development chain. Most plausibly it would apply at the lowest, most basic level, where researchers would share knowledge about the theoretical uses of specific chemicals and test these using computer models.

Once a set of potentially useful chemicals has been identified for the treatment of a disease, it would then be necessary to carry out more rigorous testing, which at some stage would entail conducting 'wet' clinical trials. Such trials require substantial resources (including lab animals and expensive and complex equipment, not to mention salaries of well-educated researchers), so the question would then arise as to how these trials would be funded, which brings the discussion back to intellectual property rights.

In the context of open source software, there are several competing IP models. The most popular of which are the Gnu General Public Licence (GPL) and the Berkeley Software Distribution (BSD) model. Under a GPL, innovators who alter GPL software must apply an identical GPL to the software they create, which means they cannot benefit from mass marketing the software – rather, they benefit financially (if at all) from developing bespoke software or selling support services associated with the software.

Under a BSD licence, however, downstream innovators are permitted to protect any software they develop using intellectual property. Given the objective of developing new drugs for the diseases of poverty, it seems clear that the appropriate licence type for such activities would be a BSD, since this would give companies a mechanism to benefit from the investments they make in drug development.

Restricting the granting of patents on 'Me-too' drugs

One oft-cited criticism of the current pharmaceutical research and development paradigm is that it is both wasteful and duplicative, with too many resources being devoted to minor modifications to existing treatments, and not enough on developing genuinely novel treatments (e.g. Angell, 2004). They refer disparagingly to 'me-too' drugs, by which they generally mean drugs that have a similar molecular structure to an existing drug used to treat a particular condition, although this is not always the case.

To rectify this situation, it has been proposed that patents should not be granted to such 'me-too' drugs. The

premise of this proposal is that more resources will then be channelled towards research on 'breakthrough' discoveries in the hope that it will generate more novel, 'blockbuster' drugs.

However, this proposal is based on a fundamental misunderstanding of the nature of innovation, which necessarily is an incremental process (Wertheimer & Santella, 2005). The advantages of incremental improvements on existing drugs are paramount to overall increases in the quality of health care. As the pharmaceutical industry has developed over time, classes of drugs have expanded to provide doctors with the tools they need to treat diverse patient groups.

While critics claim that there are too many similar drugs, drugs based on incremental improvements often represent advances in safety and efficacy, along with providing new formulations and dosing options that significantly increase patient compliance. From an economic perspective, expanding drug classes represent the possibility of lower drug prices as competition between manufacturers is increased. Additionally, pharmaceutical companies depend on incremental innovations to provide the revenue that will support the development of more financially risky 'block-buster' drugs. Policies aimed at curbing incremental innovation will ultimately lead to a reduction in the overall quality of existing drug classes and may ultimately curb the creation of novel drugs.

The evolution of pharmaceutical therapies

Like the evolution of the human species, technological advances tend to occur incrementally, one step at a time. As a result, progress is made over time, as many small steps equal one giant leap. Like other technological and value-added industries, the pharmaceutical industry depends on these small steps for the creation of blockbuster drugs, as these drugs often stem from a large number of small innovations.

Table 3 **New fomulations with extended uses**

Drug	*Original indication*	*New formulation*	*Extended uses*
Antibiotics	Parenteral use only	Oral preparations	Bowel preparation, hepatic coma
		Topical forms	Skin, eye, ear infections
		Inhaled use	Cystic fibrosis
Corticosteroids	Steroid-responsive conditions	Intravenous bolus injections	Same use with greater efficacy and safety
		Enemas	Ulcerative colitis
Cromolyn sodium	Prophylaxis of asthma by aerosol	Nasal insufflation	Hay fever
	Eye drops		Hay fever
Glyceryl trinitrate	Angina	Transdermal patch	Greater efficacy
Heparin	Intravenous treatment for venous thrombosis	Subcutaneous low-dose	Prophylaxis of post-operative venous thrombosis
Medroxyprogesterone acetate	Endometriosis, etc	Depot injection	Long-term contraception
Morphine	Pain	Slow-release injection	Prolonged action
		Epidural injection	Regional analgesia
Pilocarpine	Glaucoma	'Ocuserts'	Prolonged action
Vancornycin	Parenteral antibiotic	Oil-paste (Matrigel) capsules	Antibiotic-induced pseudomernbranous colitis

Source: Snell, E, "Postmarketing Development of Medicines," *Pharmacy International*, 7(2), 33–37, 1986

Table 4 **Advantages of selected beta-blockers**

	Preserves blood flow to and from the kidneys	*Once daily dosing*	*Reduces mortality after heart attack*	*No change in blood cholesterol levels*	*Selectively targets B1 receptors*	*Equal effectiveness in blacks and whites*	*ISA*[3]	*Very low central nervous system penetration*	*Relaxes blood vessels resulting in improved blood flow*
Acebutolol		✓			✓		✓		
Atenolol		✓			✓			✓	
Labetalol	✓			✓		✓			✓
Metoprolol		✓[1]	✓		✓				
Nadolol	✓	✓						✓	
Pindolol	✓			✓			✓		
Propranolol		✓[2]	✓						
Timolol			✓					✓	

1 Once a day for hypertension.
2 For controlled-release preparation only.
3 Drug possesses 'intrinsic sympathomimetic activity', which allows blockade of excess stimulation of the heart by sympathetic nerves while maintaining adequate blood flow through the heart and peripheral blood vessels.
Source: Frishman, W, "Clinical differences between beta-adrenergic blocking agents: implications for therapeutic substitution", *American Heart Journal*, 113, 1190–1198, 1987

It also depends on these steps for the creation of drugs that provide a slight improvement on existing drugs, thereby adding to a drug class, increasing competition among drugs, and creating a stimulus for further innovation. As the National Research Council has observed, "the cumulative effect of numerous minor incremental innovations can sometimes be more transforming and have more economic impact than a few radical innovations or 'technological breakthroughs'" (National Research Council, 1996). The net effect of increasing the number of drugs through innovation leads to advances in safety, efficacy, selectivity, and utility of drugs within a specific class.

While critics have concluded that incremental innovations do little more than produce more of the same to increase industry profits, an examination of the major classes of drugs yields a much different picture. The improvements made to the classes of antihistamines, antibiotics and beta-blockers provide good examples of the net effects of stepwise innovation. The following diseases and respective treatments are examples of incremental innovation in practice.

Trachoma

Trachoma is a preventable disease that predominately affects rural people who suffer overcrowded living conditions. Trachoma is an infectious disease of the eye caused by the bacterium *Chlamydia trachomatis*. The bacteria can be spread easily on an infected person's hands or clothing, or may be carried by flies that have come in contact with discharge from the eyes or nose of an infected person. Untreated, it can cause blindness. Currently, 8 million people are visually impaired as a result of trachoma, and 84 million suffer from active infection.[52]

For many years, existing antibiotic treatments for trachoma were inappropriate for the conditions faced by many sufferers of the disease. The existing antibiotic, *Zithromax*, produced severe gastro-intestinal side effects, which meant a small dose had to be delivered daily over a period of three to five days. Patients in poorer countries had difficulty adhering to the regimen, which in turn presented the possibility of drug resistance.

Scientists hoped to overcome these problems by producing a slight reformulation of the drug – *Zithromax SR* – with the intention of creating a single dose

treatment. Whereas the original formulation was a multi-dose 1.5g pill, the researchers were able to turn the drug into a 2g single-dose fluid suspension, enabling a far higher rate of adherence among patients. This incremental innovation has thereby minimised the chances of drug resistant strains of the trachoma bacteria developing, as well as providing a clinically superior product.

Antihistamines

The original generation of antihistamines were effective therapies but entailed a host of negative side effects, including anticholinergic effects, penetration of the blood-brain barrier, and severe drowsiness. Additionally, the therapeutic effect of these drugs dissipated rapidly thus necessitating frequent dosing. The second-generation antihistamines, (i.e. astemizole, loratadine, cetirizine) constituted significant improvements on the originators. These drugs significantly extended the therapeutic effect, reduced penetration of the blood-brain barrier, created no anticholinergic effects, and drastically reduced drowsiness. A new generation of antihistamines (i.e. Allegra), developed from the active metabolites of the second-generation drugs, has led to even greater therapeutic value with increased safety and efficacy.

Beta-blockers

The development of beta-blockers into a wide-ranging diverse class of drugs allows physicians to provide individualised treatment. Because no single beta-blocker works well for all patients, it is necessary for physicians to have many options at their disposal. After the introduction of propranolol, many new generations have advanced in selectivity and provided many diverse agents with vastly differencing therapeutic characteristics (i.e. atenolol, bisoprolol, metaprolol, betaxolol). These new drugs show differences in preserving renal blood flow, dosing schedule, changes in serum lipid levels, sympathomimetic activity, central nervous system penetration, vasodilation, and effect on different racial groups. Often, matching a patient to the right beta-blocker is a process of trial and error, as some products simply work for some patients better than others. Together, these many options provide an increased net therapeutic value

Economic implications

Perhaps the most vehement criticism alleged of 'me-too' drugs is that they siphon money away from research that could otherwise be devoted to the creation of novel breakthrough drugs. This assumption is incorrect for a host of reasons, the most important of which is that the pharmaceutical industry depends on incremental innovations to provide the revenue to support the development of breakthrough drugs. Additionally, while it is unrealistic to presume that every incremental innovation leads to cost savings, the sum of all drug innovations can result in cost savings in the following areas:

- Reduced overall treatment costs.
- Shortened or eliminated hospital stays.
- Increased worker productivity and less absenteeism.
- Reduced drug costs from increased competition among manufacturers.

Opponents of me-too drugs argue that limitations on incremental drug innovations will lead to increased investment in 'blockbuster' drugs – but it is not clear how this will come about. The evidence is in the other direction. They implicitly advocate the idea that pharmaceutical companies should invest all their capital in high-risk projects. Judging from the historical evidence, such projects are more likely to fail than succeed. That seems to be a recipe for disaster, or at least could reduce significantly the development of all new drugs, blockbusters and 'me-toos' alike.

The current system, while far from perfect, at least enables pharmaceutical companies to hold diversified portfolios of new chemical entities, leading to pipelines of mainly lower-risk incrementally innovative drugs, the income from which helps provide the capital for investment in more risky blockbusters.

Discussion

This chapter has considered various possible means of increasing the number of medicines for the diseases of poverty. Particular importance has been given to mechanisms that might enhance the incentives of private-

sector R&D companies to invest in developing such drugs. Among the better ideas in that regard are:

- Patent extensions – as long as they are applied to a range of drugs and last for only a relatively brief period.
- Tax and regulatory breaks, such as those provided in the US to 'orphan' drugs.
- Public-private partnerships, especially where the public sector involvement comes primarily in the form of support and co-ordination of basic research, as with the US NIH.

Other methods, such as advance purchase commitments and similar prize-like schemes, while inappropriate as a general means of incentivising innovation, may also have a role to play in incentivising the development of drugs for specific diseases.

We are particularly concerned, however, at several proposals that ostensibly intend to enhance innovation but in practice may have the opposite effect. First, restricting the award of patents to 'blockbuster' drugs would seem to be counterproductive on two counts: it would limit both the extent to which other companies could 'invent around' the molecule to develop competing drugs in a class and it would discourage the development of follow-on innovations that might be superior. The result would be fewer, more expensive drugs – quite the opposite of what is intended.

Second, promoting a combination of greater public funding of research and development, to take place in an 'open source' environment would likely suffer from a combination of the problems that direct government funding of pharmaceutical R&D has historically suffered, namely a lack of appropriate incentives to develop effective and efficient molecules, combined with a weakening of the incentives to take drugs through the necessary regulatory stages. While there may be some merit in open source drug development, this would most likely be the case if the open source licenses permit companies investing in drug trials to capture the benefits from their investments.

5

Conclusions and policy recommendations

In this report we have attempted to present a dispassionate and apolitical survey of the challenges facing policymakers charged with formulating public policy for the diseases of poverty. We have reached the following broad conclusions:

The prevalence of the diseases of poverty

- Much of the disease burden of lower income countries is caused by diseases that could be prevented or cured with existing technologies. However, these technologies – including many inexpensive, off-patent medicines – are not widely available in many places where they would be most beneficial.
- Public sector provision of medical care often has little impact on access to medicines, especially in rural areas. Typically the focus of such provision is on the wealthier urban middle class Yet the majority of the World's poorest people live in rural areas.
- The WHO's troubled '3 by 5' HIV treatment programme and Roll Back Malaria programme are examples of grandiose ambition trumping practical considerations. Worse, these kinds of programmes may have contributed to increasing drug resistance.
- The nature and spread of diseases suffered in both rich and poor countries is converging rapidly. In absolute terms, non-communicable diseases now kill greater numbers of people in the lower-income countries than they do in high-income. Cardiovascular diseases are now among the most significant killers in lower-income countries. It is important that current and future R&D for these diseases is encouraged.

Addressing the diseases of poverty

- A large proportion of the disease burden in low-income countries could be reduced by the effective distribution of medicines that are currently available and inexpensive.
- However, this is held up by several factors not least of which is poverty itself, which means that many people simply cannot afford even basic medicines. Poverty also leads to poor nutrition and generally unhealthy living conditions.
- It is unlikely that good health will ever be sustained without long-term wealth creation that can pay for the ongoing improvements in water, sanitation, nutrition, living conditions, health education and hospitals which are vital for the control of diseases such as malaria, tuberculosis and AIDS.
- Meanwhile, economic growth is most likely to occur on a sustainable basis when societies have institutions which support economic freedom (including secure, transferable and enforceable property rights, freedom of contract and the rule of law).
- Unfortunately, the governments of poor countries continue to hinder the creation of wealth, imposing obstacles in the way of owning and transferring property, imposing unnecessary regulatory barriers on entrepreneurs and businesses, and restricting trade through extortionate tariffs.

Research and development for the diseases of poverty

- Research and development activity around the diseases of poverty is currently taking place at unprecedented levels, largely as a result of the creation of Public Private Partnerships. This R&D

activity is expected to increase over the next few years as these PPPs become more established.

- Most important advances in pharmacology have been made with wealthy markets in mind. These range from such things as vaccines for childhood diseases to ARV drugs. Lower-income countries have benefited enormously from this technology transfer and will continue to do so in the future.
- However, such countries often have not benefited from the full potential of modern drugs because of a number of self-generated policy failures that actively impede access to medicines. These include excessive tariffs on imported drugs and taxes on both imported and domestically-produced drugs, a range of non-tariff barriers, weak healthcare systems, and inadequate risk pooling mechanisms (or health insurance).

Innovation

- This lack of access has the follow-on effect of dampening demand for medicines, making commercial activity in this area less attractive. Commercial drug developers are unlikely to invest large amounts of capital in a potential new drug if it is unlikely to penetrate its intended market.
- Weak intellectual property legislation in countries with incipient or extant knowledge-based industries acts as a serious disincentive on R&D into the diseases of poverty, not least because it jeopardises the ability to generate enough sales to cover the extremely high costs of innovation.

  This is particularly true of highly politicised diseases such as HIV/AIDS; with countries such as Brazil threatening to implement compulsory licenses for ARVs, it becomes more difficult for R&D companies to devote resources to searching for new medicines.

  Strong intellectual property legislation can also go some way to encouraging the development of an indigenous R&D industry in countries where it currently does not exist. As India comes to terms with its recently enacted patent legislation, for example, more companies are turning to value-added R&D work, rather than merely producing copies. These companies are also likely to find commercial benefit in developing drugs for diseases prevalent among local populations, which, due to their lower cost base, can be developed at prices far lower than equivalent development in wealthy countries.
- Unfortunately, there are a number of elements in the public policy mix which actively discourage commercial R&D for diseases that mainly afflict lower income countries. These include: burdensome pre-market regulations which drive up the cost of development; non-tariff trade barriers which erode the ability of R&D companies to market their products overseas; price controls which serve to discourage companies from serving markets where they are in place; an inability to enact and enforce price differentiation strategies, which prevents companies from recouping sufficient sums to allow them to sell their products at cost price in the poorest countries; and the threat of compulsory licenses by countries such as Brazil, which interrupts commercial pricing strategies, and adds an unpalatable risk to R&D.

Current proposals scrutinised

- Notwithstanding these barriers to access and innovation, there is a need for new medicines to be developed for the diseases of poverty, not least because of increasing drug resistance. However, many of the proposals on the table to create incentives for R&D into such new drugs, while not without their merits, also suffer from significant flaws.
- One such suggestion is to increase direct, public funding for private or public entities engaged in such R&D. However, the evidence suggests that such spending is wasteful, inefficient and unlikely to produce results.
- Transferable patent extensions may work but need to be carefully thought through. A scheme that allowed a drug company to extend the patent on a single blockbuster for a year or more, for example, would effectively force the users of that drug to pay for the development of a drug for a completely different disease. This is ethically dubious and would likely be

met with fierce resistance by patient groups. If, however, the patent extension was spread more thinly, for example by granting a short patent extension to many drugs, then these concerns would likely fall away.

- Advance Purchase Commitments have been accepted by the G8 as an appropriate mechanism for generating a malaria vaccine. However, it is far from clear that such schemes are either efficient or workable. Because the value of the end product must be determined by a committee rather than by market processes, it is likely that the cost of the final product will be inflated. Furthermore, because they are a 'winner takes all' prize, APCs will stifle incremental, follow-on competition, meaning that few improvements will be made to the final product. This will have significant implications in case of resistance or special clinical requirements for subpopulations. Finally, the historical record of prizes – of which APCs are a particular kind – is far from encouraging.
- Orphan drug legislation has been moderately successful in encouraging drug companies to develop drugs for 'orphan' diseases in the US, largely by providing a favourable tax and fast-track regulatory environment. This could feasibly be replicated for R&D into the diseases of poverty.
- The success of open source in software development has led some to argue that it could be replicated in drug development. While this may be a workable model for the early stages of development, open source is unlikely to provide the large amounts of capital and labour required to take a drug through extensive clinical trials.
- Proposals that seek to restrict the granting of patents for so-called 'me-too' drugs misunderstand the incremental nature of innovation. The vast majority of drugs that exist today are incremental improvements on the drugs that preceded them. The existence of many similar drugs in the same class is vital for improving safety, efficacy, selectivity, and utility of drugs within a specific class.
- Private Public Partnerships are proving to be an effective way to direct R&D towards the diseases of poverty. PPPs are largely responsible for the current, unprecedented levels of research and development activity around the diseases of poverty. At the end of 2004, over 60 neglected disease drug development projects were in progress, the highest level to date. Furthermore, research shows that these partnerships are conducting their work more quickly and cheaply than industry standards, while the costs are being largely borne by the private sector.
- There is some concern from researchers that introducing policies designed to 'kick start' innovation from scratch will undermine the excellent progress being made by PPPs. If companies are presented with pseudo-market mechanisms such as APCs, for example, there is a risk they will divert resources away from the successful, effective and cheap PPP ventures towards these more risky projects.
- While there are genuine concerns regarding certain aspects of the intellectual property system (such as the granting of patents for research tools and genetic sequences), several of the proposed 'solutions' would have adverse effects that are likely worse than the alleged problem being addressed. In particular, creating a stronger obligation to provide pre-grant review would increase the bureaucracy of the patent system. Meanwhile, introducing a requirement of 'efficacy' (over and above the standard 'utility' or 'capable of industrial application') would lead to arbitrariness and would likely lead to many molecules not undergoing development because of a lack of patent protection.

Recommendations

Many of the push and pull mechanisms examined have some merit in stimulating research into diseases endemic to poorer countries. However, all of these solutions must only be considered as short-term expedients, because they do little to alter the fundamental problems associated with developing and delivering drugs for the diseases of poverty.

In the longer term, we believe that governments must create environments that are conducive to the fragile process of innovation. This is the only way to bolster the pipeline of new drugs in a sustainable manner.

But if health distribution and communications channels are ineffective, new medicines may not reach new patients at all. This will dampen the overall potential of new medicines, so it is essential that barriers to access be removed where they exist.

Furthermore, the lack of proper healthcare systems in poor countries makes it difficult to glean data about the disease profile of a country, and this undermines the ability of companies and governments to determine what new medicines are required. This in turn makes effective research prioritisation next to impossible.

We believe that concrete steps to rectify these areas could include the following:

- The governments of poor countries must, as a priority, remove barriers to the provision of healthcare, especially taxes, tariffs and regulatory barriers that currently prevent the poor from obtaining essential medicines.
- The governments of poor countries should improve the institutional environment more generally, so that people are able to generate wealth and thereby ensure that healthcare systems become self-sustaining – and provide a strong demand driver for the development of new drugs. This would include, *inter alia:*
  - Clearly defined, readily enforceable and transferable property rights.
  - Rule of law, backed by an independent and impartial judiciary.
  - An IP system that meets at least minimum standards, such as those set in the TRIPS Agreement.
- Higher-income countries should provide a regulatory and tax environment that nurtures PPPs and pure private sector development of drugs for the diseases of poverty. This might include, i*nter alia:*
  - Fast-track approval for drugs for diseases of poverty.
  - Tax-breaks for research into such drugs.
  - Patent extensions to a range of drugs in home markets when companies develop an effective drug for a poverty disease.
- Countries with slow and inefficient patent offices might introduce incentive-based pay schemes (combined with appropriate quality controls), or contract out services to the private sector (combined with clear quantity and quality controls). Such changes would likely improve throughput and thereby increase both the incentives to innovate and access to new medicines.
- Likewise, it may be worth merging patent offices in certain regions in order to reduce the degree of redundant processing.
- All countries should consider improving the efficiency and effectiveness of the their drug regulatory agencies, so that companies developing new drugs are subject to fewer and less arbitrary restrictions on the marketing of their products, while safeguarding consumers. This might entail:
  - Creating competing drug regulatory bodies and certifiers. Such accountable, competitive regulators would set the standards of regulation at levels demanded by those making choices about drug regimens. For many drugs, this would mean swifter approvals and a reduction in development costs, leading to an increase in the number of drugs developed for most diseases – especially those which affect the poorest and those which affect smaller populations – while also reducing the price of medicines to all.[53]
  - Guaranteeing longer periods of data exclusivity. This would enhance the incentives of companies to develop new drugs.
- Governments should avoid creating a new intergovernmental body for the promotion of drug development, since such body is unlikely to be an efficient vehicle for increasing drug research and development. Indeed, it would likely be counterproductive, diverting resources away from more productive uses, such as current efforts by several PPPs, which have already achieved a great deal of success in developing medicines specifically for the diseases of poverty.

Finally, we find it curious that the WHO should have convened a commission in an area outside of its remit when it has failed on many occasions to fulfil its basic functions. As this report has demonstrated, the WHO has

failed to provide adequate leadership in tackling the most pressing health problems facing lower-income countries. In the cases of malaria and HIV/AIDS particularly, the WHO's failure to implement cost-effective preventative strategies has resulted in an unnecessarily high burden of disease, economic loss and human suffering. Meanwhile, access to currently existing medicines is unacceptably low in many parts of the world – a factor that contributes, in part, to the high disease burden from preventable diseases.

Given its lamentable track record in fulfilling the aims of its constitution, it is unclear why the WHO is dedicating scarce resources to considering issues that are peripheral to its remit, such as intellectual property – especially when there are other UN fora, such as the World Intellectual Property Organization (WIPO) that possess a specific mandate to deal with IP issues. We recommend, therefore that WHO should desist from this activity and refocus its activities on concerns that are both more pressing and for which it has – at least ostensibly – greater expertise.

Appendix

Figure 1 **Market equilibrium**

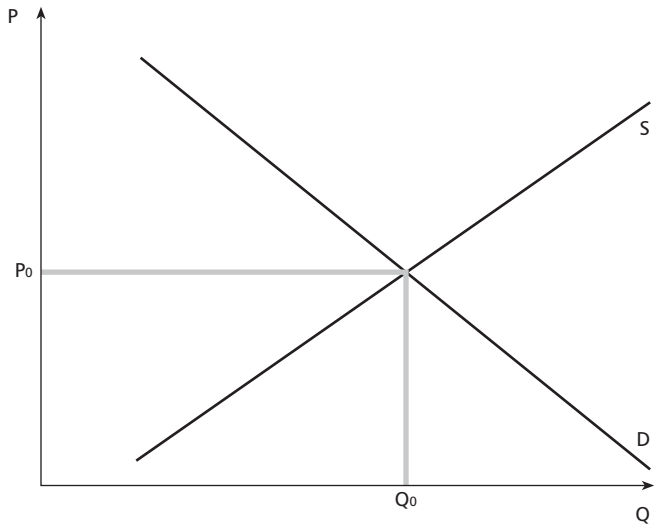
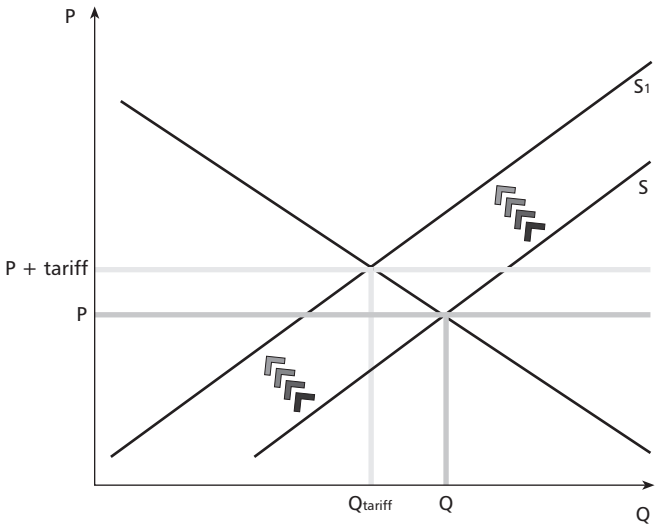


Figure 1 shows consumer willingness to pay, represented by the 'demand' curve, D, and industry willingness to supply, represented by the 'supply' curve, S. The intersection of these two curves shows the total quantity that will be supplied, Q_0 and the minimum price charged, P_0.

Figure 2 **Effect of taxes and tariffs on demand for medicines**



If a government imposes a tax on a medicine, this raises the minimum price artificially. Figure 2 shows the effect of adding such a tax; the supply curve is effectively shifted inwards because suppliers must now add the tax to the amount that they charge. As a result, the amount supplied falls from Q_0 to Q_{tariff}.

Figure 3 **The impact of a rightward shift in the demand curve**

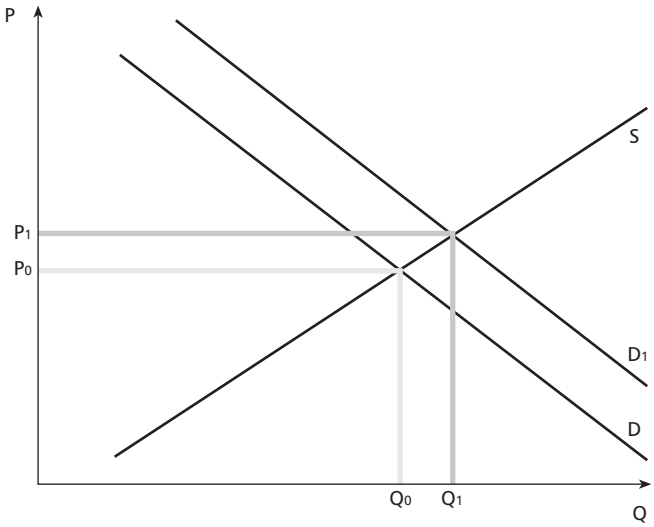


Figure 4 **The impact of a rightward shift in the supply curve**

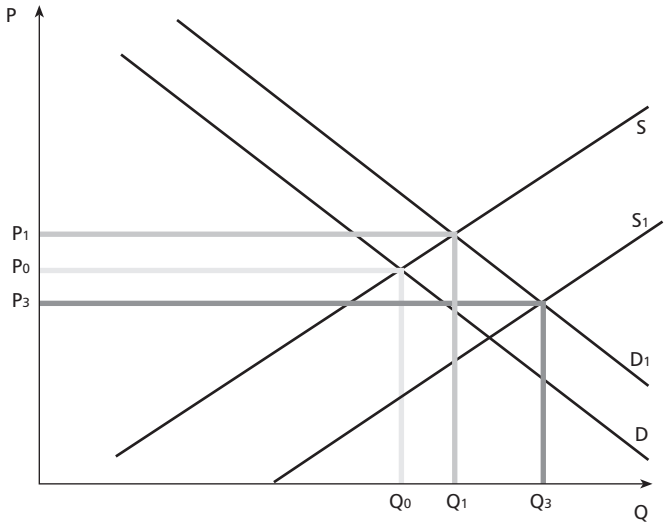


Figure 3 shows that when consumer willingness to pay increases (for example as a result of a rise in income), the demand curve shifts to the right. This leads to an increase in the amount supplied (from Q_0 to Q_1) and also to an increase in the minimum price (from P_0 to P_1). This is because the supply has been met by moving along the original supply curve, for which the cost of producing an incremental unit is assumed to rise as output rises — because more expensive production methods have to be brought on-stream.

However, the rise in price (as a result of the expansion in the demand curve in Figure 3) is likely to be seen by entrepreneurs as an opportunity to make money by supplying the market using new technologies (these might be, for example, new production technologies, or they might be new drugs in the same class). As those entrepreneurs enter the market, supply increases to Q_3, and the price falls to P_3. This can be represented as a rightward shift in the supply curve (Figure 4).

Figure 5 **Perfect market segmentation**

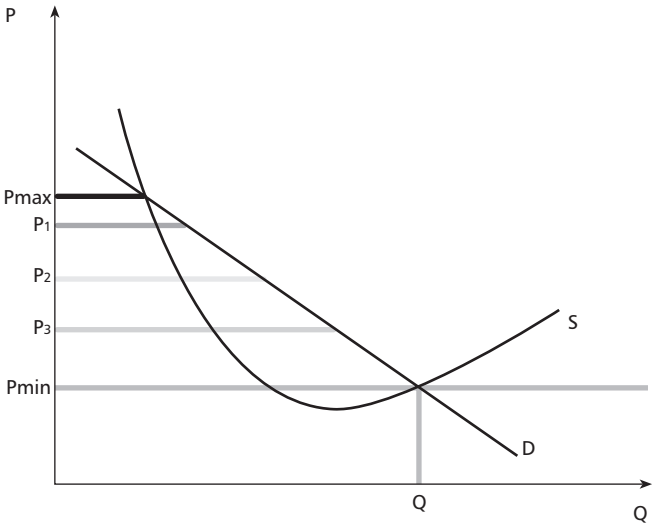
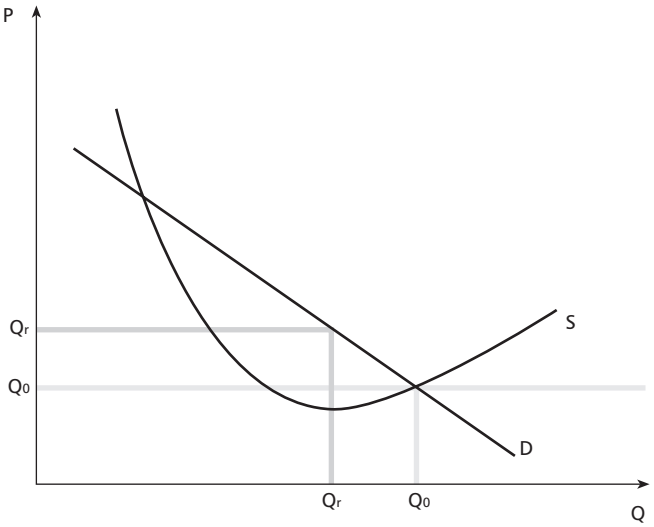


Figure 6 **Regulated market**



If a supplier has an element of market power (for example as a result of the temporary market exclusivity conferred by a patent), then in principle he is able to set prices and will do so in such a way as to maximise profits. The textbook economics analysis of such situations assumes that the supplier will choose only one price, which will be higher than the marginal cost of production. However, if the supplier is able to segment the market perfectly, then he will sell at a wide range of different prices to different consumers and will maximise profits by setting the minimum price (Pmin) at which he sells just above the marginal cost of production and the maximum price at Pmax. He will then sell total quantity Q, which is the same as the perfectly competitive quantity. This is shown in Figure 5.

The quantity sold under a regulated market, Q_r, is lower than the quantity sold under a segmented market, Q_0, where the firm is able to price its product based on the willingness to pay of different groups of consumers. The price paid by the poorest consumer in the regulated market, P_r, is higher than the lowest price charged in a segmented market, P_0.

Notes

1 CIPIH Framework Paper, July 2004: www.who.int/intellectualproperty/documents/framework_paper/en/index.html

2 http://www.who.int/mediacentre/factsheets/fs117/en/

3 http://www.who.int/vaccines/en/pertussis.shtml

4 http://www.who.int/mediacentre/factsheets/fs101/en/

5 United States Leadership Against HIV/AIDS, Tuberculosis, and Malaria Act of 2003.

6 http://online.wsj.com/article/0,,SB111644800426237250,00.html

7 WHO/CDS/WHOPES/GCDPP/2004.6, A generic risk assessment model for insecticide treatment and subsequent use of mosquito nets.

8 http://www.cdc.gov/malaria/control_prevention/vector_control.htm

9 http://www.rotavirusvaccine.org/vaccine-facts.htm

10 Jabu Mhlabane. Nearly 50 Mpumalanga doctors implicated in medicine theft (Middelburg, South Africa: *African Eye News Service, 13 February 2003). (Published on the website of LowveldInfo.com.)*

11 The study assessed the size and impact of tariffs and taxes on drugs imported from the EU; taxes and tariffs on drugs imported from elsewhere may be subject to different rates of taxes and tariffs.

12 Poor countries are not members of the WTO Pharmaceutical Agreement, a 22 member agreement, concluded during the Uruguay Round, which has led to the reciprocal elimination of tariffs (dubbed 'zero-for-zero') on approximately 7,000 products (European Commission, 2003 and 2002).

13 The East African Community (EAC) is the regional intergovernmental organisation of the Republics of Kenya, Uganda and the United Republic of Tanzania with its headquarters in Arusha, Tanzania. The EAC website is: http://www.eac.int/

14 Information regarding the EAC Customs Union Tariffs scheme can be accessed at: http://www.eac.int/EAC_customs_U.htm

15 http://allafrica.com/stories/200502230903.html

16 European Commission, 2003. Applied customs rates were found for each of 27 HS numbers. To obtain and average customs rate per country, these numbers were arithmetically added without weighting them. The same process was used to calculate the average rates of VAT and other duties.

17 While there are some countries where the costs of introducing a patent system may temporarily outweigh the benefits, this applies only to those countries without a substantial knowledge-based industry. For those countries with incipient or extant knowledge-based industries, such as India, China, Brazil and South Africa, the benefits of introducing a patent system will quickly outweigh the costs.

18 McArthur (1999) shows that in industries with relatively stringent protection for intellectual property, capital spending is higher, the demand for high quality goods for export and the ratio of skilled to unskilled workers both increase over time. Those same incentives that exist for investment in industries that do enjoy relatively high levels of intellectual property protection tend not to exist when that protection does not exist or is abandoned. McArthur, W. M.D., *Intellectual Property Rights and the Pharmaceutical Industry*, The Fraser Institute, 1999, pp. 85–104.

19 SCRIP data.

20 http://www.businessweek.com/magazine/content/05_16/b3929068.htm

21 Indian drug research at a fraction of global costs, Scrip no.2863, 2 July 2003.

22 http://www.advocate.com/news_detail_ektid19293.asp

23 http://www.sedb.com/edbcorp/sg/en_uk/index/in_the_news/press_releases/2004/singapore_s_biomedical.html

24 http://www.rbm.who.int/cmc_upload/0/000/015/364/RBMInfosheet_9.htm

25 http://drugresearcher.com/news/printNewsBis.asp?id=57722

26 Or alternatively: novelty, inventive step and industrial application.

27 In the context of the debates over patents on genetic sequences and research tools, if some countries allow patents and others don't, then – other things being equal – over time it will become clear which countries are more conducive to high-levels of research and development into down-stream innovations. Of course not all other things are equal, but to the extent that this competition is already taking place, the winner seems to be the country with the broader patent system: the United States. Time will tell.

28 Common practice for the Food and Drug Administration in the United States is 5 years, which is also the period agreed upon in many of the bilateral free trade agreements it has recently signed.

29 Potential cost savings for companies relying on data would be in the order of $450 million, the average costs associated with clinical trials for each approved drug. Some estimates show that these costs have more than tripled in the past fifteen years.

30 When data exclusivity is weak, it can also drive research-based pharmaceutical research industries out, as has happened in the past few years in Israel. A once thriving research destination, the lack of data exclusivity – the result of a powerful generics lobby – had driven research elsewhere. In September 2005, the legislation was changed to provide some data protection.

31 In legal terms, the specific element that is crucial to the firm's ability to price differentiate within a market is the international patent exhaustion principle. If patent rights are exhaustible the patentee must renounce the right to its product the moment it is first sold, giving the first purchaser the ability to potentially resell at a higher price. The TRIPS agreement does little to clear up this pressing issue. (http://www.wto.org/english/tratop_e/trips_e/factsheet_pharm02_e.htm)

32 A good example of successful price discrimination without re-exportation comes from the example of bronchodilators in South Africa. Here, Government purchases accounted for 66 percent of sales volume, but only 33 percent of revenues. In this case patents show that, if parallel importation is controlled for, good health can be promoted. Reekie, W.D., "South Africa's Battle with AIDS and Drug Prices", National Center for Policy Analysis, Dallas, TX, Brief 334, 2000.

33 http://www.freemarketfoundation.com/ShowArticle.asp?ArticleType=Publication&ArticleID=1093

34 The most recent example comes from Brazil, where the head of the country's AIDS program cited an increasingly high percentage of its AIDS budget, which is

designed to offer Brazilians with the disease (some 600,000) free treatment, had to be devoted to pharmaceutical purchases. Because of this, Brazil threatened to issue compulsory licenses on the key drugs that combine to form anti-retro viral treatments. Accessed 06/01/2005

35 'Neglected diseases' are defined by the WHO as African Trypanosomiasis, Leishmaniasis and Chagas disease.

36 The British government, for example, gives specific tax breaks to companies who conduct R&D:

37 Hubbard, T., Love J., 2004. "A New Trade Framework for Global Healthcare R&D." *PloS Biology,* February, 2004;2(2):147–150. Another direct funding suggestion from US senator Kucinich: (accessed 10 March 05).

38 http://www.aeras.org/

39 http://idri.org/page.php?pg_page_id=1

40 Drugs in development by the following PPPs: Bio Ventures for Global Health, Pharmaprojects, MMV, GATB, DNDi.

41 *Ibid*.

42 http://www.cgdev.org/globalhealth/Making%20Markets%20for%20Vaccines%20Consultation%20Draft_final.pdf

43 For an interesting discussion of the X-Prize and other prizes both historical (such as the 1920s Orteig Prize for aircraft design) and current (such as the Methuselah Prize for doubling the lifespan of lab rats) see the Futurepundit website at: http://www.futurepundit.com/archives/002384.html

44 According to the FDA: http://www.fda.gov/orphan/oda.htm

45 Rare diseases are typically defined differently in the countries that have implemented Orphan drug legislation. A list of the different definitions in the US, the EU, Japan, and Australia is provided by Orphan-europe.com accessible at: http://www.orphan-europe.com/1038580716.html

46 Some numbers put the tax break on Orphan disease research investments as high as 50 percent. http://rarediseases.about.com/library/weekly/aa053000a.htm

47 Researchers can access the latest work completed on orphan diseases at the National Organization for Rare Disorders (NORD), accessed here: http://rarediseases.about.com/gi/dynamic/offsite.htm?site=http://www.rarediseases.org/search/noddsearch.html

48 "Historically, the approval time for orphan products as a group has been considerably shorter than the approval time for other drugs." Accessed at: http://www.fda.gov/orphan/faq/

49 The amended version of the text of the Orphan Drug Act are posted here: http://www.fda.gov/orphan/oda.htm

50 A good example of the Open-source suggestion was explored by the authors in an article published in PLoS Medicine. See Maurer, S. M., Rai, A., & Sali, A. (2004). "Finding Cures for Tropical Diseases: Is Open Source an Answer", *PLoS Medicine*, Dec.

51 Information about the Firefox 1.0 is available at http://www.mozilla.org/

52 http://www.trachoma.org/trachoma.php

53 As noted above, public health would be safeguarded by the desire of these agencies to defend their own reputations. The importance of reputation in maintaining clients and attracting new ones, the existence of a free press engaging in investigative journalism, and expected penalties through the legal system for corrupt and dangerous decisions by these regulators, should lead to a well-functioning market in drug approval. An accountable drug approval agency that bends to pressure from pharmaceutical companies, for example, would be quickly exposed, and the marketability of their future products would suffer.

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Civil Society Report on Intellectual Property, Innovation and Health

The relationship between intellectual property rights, innovation and health has become controversial, with many blaming patents for the very low rates of access to medicines in poor countries. Meanwhile, it has been observed that current patterns of research and development do not precisely reflect the global disease burden.

This report is a collaborative effort of a global coalition of civil society groups that seeks to shed light on these issues. We have sought to address complex and difficult questions, such as "What are the best ways to encourage the development of new drugs for diseases endemic to lower-income countries?" and "What role does intellectual property play in such development?"

When these issues are debated in intergovernmental fora, they are often obfuscated by the need to balance conflicting political agendas. This report attempts to overcome these shortcomings by employing dispassionate theoretical and empirical analysis free of political considerations.

The report finds that much of the disease burden of lower-income countries could be alleviated if existing treatments and techniques were properly deployed. While no intellectual property system is perfect and checks and balances are needed, patents are not a substantial hindrance to access. On the contrary, when there is effective demand for drugs, patents act as a strong stimulus to innovation.

Unfortunately, government failures hinder both the distribution of existing medicines and the process of innovation. These failures range from tariffs and taxes, to stultifying pre-market regulations. If governments are serious about increasing access to medicine, then they should remove these barriers.

Action Research and Community Health, India

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