Journal of Economic Perspectives—Volume 16, Number 4—Fall 2002—Pages 67–90

Pharmaceuticals and the Developing World

Michael Kremer

Pharmaceuticals have brought tremendous health benefits to developing countries, but existing pharmaceuticals are often underused or misused, and pharmaceutical R&D on health problems specific to poor countries is woefully inadequate.

The role of pharmaceuticals and medical technology in improving health in developing countries stands in contrast to the historical experience of the developed countries. Historically, health in currently developed countries improved largely due to higher incomes and consequent improvements in nutrition, sanitation and water supplies. Fogel (1986) finds that half of the decline in standardized British death rates and 70 percent of the decline in standardized American death rates between 1700 and 1980 occurred before 1911, in an era with few effective medicines. However, modern medical technologies allow tremendous improvements in health even at low income levels. The outward shift of the technological frontier is illustrated by Vietnam, which has a life expectancy of 69 years despite a per capita income that according to official statistics is less than one-tenth that of the United States in 1900, which had a 47-year life expectancy.[1] To take another example, per capita GDP in low-income sub-Saharan African nations decreased 13 percent from 1972 through 1992, but life expectancy increased by 10 percent,

[1] Data are from Balke and Gordon (1989), Johnston and Williamson (2002), Kurian (1994) and World Bank (2001b). Even if GDP growth in the United States were underestimated by two percentage points annually, 1900 U.S. per capita GDP exceeds Vietnam's current per capita GDP.

■ *Michael Kremer is Professor of Economics, Harvard University, Cambridge, Massachusetts, Senior Fellow, The Brookings Institution, Washington, D.C., and Research Fellow, National Bureau of Economic Research, Cambridge, Massachusetts. His e-mail address is ⟨mkremer@fas.harvard.edu⟩.*

from 45 to 49 years, and infant mortality fell 30 percent, from 133 per thousand births to 93 per thousand births (World Bank, 2001b). (Unfortunately, since then, life expectancy in sub-Saharan Africa has fallen due to the AIDS pandemic.) Indeed, analysis of worldwide health trends in the twentieth century has found that most improvements resulted from technological advances rather than from income growth. Using the cross-sectional relationship between income and life expectancy, Preston (1975) estimated that income growth accounted for only 10 to 25 percent of the growth in world life expectancy between the 1930s and 1960s and suggested that the diffusion of technological advances was a major factor for the increase in life expectancy at any given income level. Jamison et al. (2001) attribute 74 percent of the decline in infant mortality rates over the period from 1962 to 1987 to technical progress, 21 percent to greater education and only about 5 percent to income growth.

While other technological improvements—such as the development of oral rehydration therapy against diarrhea and the use of radios in public health campaigns—may have played a role in improving health, the development and dissemination of pharmaceuticals has played a key role. To take one example, about three-quarters of the world's children receive a standard package of cheap, off-patent vaccines through the World Health Organization's (WHO) Expanded Program on Immunization, and these vaccines are estimated to save 3 million lives per year (Kim-Farley, 1992). Though vaccination rates are uneven around the world, the World Bank (2001b) estimates that 70 percent of infants in low-income countries received the three-dose DTP (diphtheria, tetanus and pertussis) vaccine over the period from 1995 through 1999.

Yet many people in developing countries who could benefit from pharmaceuticals do not receive them. The failure of antiretroviral therapy to reach more than a tiny fraction of people with AIDS in developing countries has attracted widespread publicity, but even medicines that are far cheaper and easier to deliver are not reaching many of the people who need them. More than a quarter of children worldwide and over half of children in some countries do not receive the vaccines that are part of WHO's Expanded Program on Immunization, although these cost only pennies per dose and require no diagnosis. Three million lives are lost annually as a result (World Bank, 2001a). Only a small fraction of children in poor countries receive the newer hepatitis B and Haemophilus influenzae b (Hib) vaccines, which cost a dollar or two per dose. One in four people worldwide suffer from intestinal worms, although treatments only need to be taken once or twice per year, have virtually no side effects, and cost less than a dollar per year. These examples suggest that while intellectual property rights undoubtedly prevent some from obtaining needed pharmaceuticals, eliminating these rights would not help the majority of those without access to drugs.

While developing countries have obtained substantial benefits from pharmaceuticals originally developed for rich country markets, little research is conducted on diseases that primarily affect poor countries, such as malaria or tuberculosis. Pecoul et al. (1999) report that of the 1,233 drugs licensed worldwide between 1975

and 1997, only 13 were for tropical diseases. Of these, five came from veterinary research, two were modifications of existing medicines, and two were produced for the U.S. military. Only four were developed by commercial pharmaceutical firms specifically for tropical diseases of humans. According to WHO (1996), 50 percent of global health research and development in 1992 was undertaken by private industry, but less than 5 percent of that was spent on diseases specific to less developed countries. Even for diseases that affect both rich and poor countries, research tends to focus on products that are best suited for use in rich countries. For example, much research is conducted on sophisticated AIDS drugs that are useful in developed countries, but are too expensive and difficult to deliver to the majority of the population in the poorest countries. Much less research is conducted on vaccines, which are typically much more feasible to deliver than drugs in developing countries, since they often require only a few doses to deliver and can be delivered by personnel with limited medical training.

The controversy over intellectual property rights for pharmaceuticals and access to antiretroviral therapies in developing countries has been the subject of much public debate recently. This article provides a broader context for the debate. It first reviews characteristics of the developing country market for pharmaceuticals, including small markets, distinct disease environments and weak health care and regulatory systems. It then outlines key market and government failures. Existing products are underused to the extent that patients do not take into account positive externalities from reducing the spread of communicable disease and that monopoly/oligopoly pricing of pharmaceuticals leads to prices greater than marginal cost; overused to the extent that patients do not take into account negative externalities from encouraging the development of drug-resistant strains; and underused, overused and misused due to asymmetric information between patients and providers and inefficient government health care delivery. R&D on new pharmaceuticals is undersupplied because competitive markets do not reward R&D expenditures and because governments face free-rider problems in supplying the global public good of R&D and have time-inconsistent preferences regarding rewarding firms for doing so.

Drawing on this background, the article then explores policy options for broadening access to pharmaceuticals and encouraging R&D on products needed in developing countries. In particular, it explores differential pricing; priorities for foreign assistance in health; the prospects for addressing pharmaceutical misuse by improving health care delivery systems; drug regulation; and the potential for rich countries or international organizations to encourage research and development on products needed by developing countries by committing to buy the products, once they are developed, and make them available to those who need them.

Characteristics of the Pharmaceutical Market in Developing Countries

The market for pharmaceuticals in developing countries differs in several ways from that in the developed world.

Table 1
World Pharmaceutical Market, Sales by Region, 1998

Region	*Percentage of Market*
United States	39.6
Europe	26.1
Japan	15.4
Latin America	7.5
Southeast Asia & China	7.0
Canada	1.9
Africa	1.0
Middle East	0.9
Australasia	0.6

Source: PhRMA (2000, adapted from Figure 7-2).

Small Markets

The market for pharmaceuticals in the poorest countries is tiny. Connecticut spends more on health than the 38 low-income countries of sub-Saharan Africa combined (World Bank, 2001b; U.S. Census, 2000). In 1998, U.S. public and private health spending constituted 13 percent of its almost $32,000 per capita income, for a total of more than $4,000 per person. In contrast, low-income sub-Saharan African nations spent only 6 percent of their average $300 per capita GDP on health, or around $18 per person (World Bank, 2001b), though developing countries spend a higher percentage of their health budgets on pharmaceuticals than do developed countries. Drug developers often do not even bother to take out patents in small, poor countries (Attaran and Gillespie-White, 2001).

Middle-income country markets are small, but comprise a significant and growing source of revenue for pharmaceutical firms. The Pharmaceutical Research and Manufacturers of America (PhRMA) estimate that while only 1 percent of their market is in Africa, including middle-income countries such as South Africa, 7 percent is in Southeast Asia and China, and 7.5 percent is in Latin America (PhRMA, 2000), as shown in Table 1.

Different Disease Environment

Developing countries face a significantly different disease environment than developed countries due to both their poverty and their geography. The burden of different diseases can be compared across countries using the concept of Disability Adjusted Life Years (Murray and Lopez, 1996). DALYs take into account not only the lives lost through disease, but also the number of years of disability caused. World Health Organization (2001) estimates imply that infectious and parasitic diseases account for one-third of the disease burden in low-income countries (in fact, for nearly half of Africa's disease burden), but only 3 percent of the burden in high-income countries, as seen in Table 2 (WHO, 2001). In contrast, the disease

Table 2
Percentage of Disease Burden

Cause	*World*	*Low-Income Countries*	*Middle-Income Countries*	*High-Income Countries*
Infectious and parasitic diseases	23.1%	33.3%	13.9%	3.0%
Tuberculosis	2.4%	2.9%	2.2%	0.3%
HIV/AIDS	6.1%	9.7%	2.6%	0.7%
Malaria	2.7%	4.5%	1.0%	0.0%
Noncommunicable conditions	46.1%	33.2%	55.5%	82.7%
Malignant neoplasms (cancers)	5.3%	2.9%	6.7%	14.4%
Cardiovascular diseases	10.3%	7.7%	12.3%	16.4%

Sources: World Health Report (2001), World Bank (2001b).

Table 3
Diseases for Which 99 Percent or More of the Global Burden Fell on Low- and Middle-Income Countries in 1990

Disease	*Disability Adjusted Life Years (Thousands, 2000)*	*Deaths per Year (2000)*
Chagas disease	680	21,299
Dengue	433	12,037
Ancylostomiasis and necatoriasis (hookworm)	1,829	5,650
Japanese encephalitis	426	3,502
Lymphatic filariasis	5,549	404
Malaria	40,213	1,079,877
Onchocerciasis (river blindness)	951	—
Schistosomiasis	1,713	11,473
Tetanus	9,766	308,662
Trachoma	1,181	14
Trichuriasis	1,640	2,123
Trypanosomiasis	1,585	49,668
Leishmaniasis	1,810	40,913
Measles	27,549	776,626
Poliomyelitis	184	675
Syphilis	5,574	196,533
Diphtheria	114	3,394
Leprosy	141	2,268
Pertussis	12,768	296,099
Diarrhoeal diseases	62,227	2,124,032

Sources: Global Burden from WHO (1996), quoted in Lanjouw and Cockburn (2001, Table 1). Figures updated from Lanjouw and Cockburn (2001), using WHO (2001).

burden in high-income countries mainly consists of noncommunicable conditions like cancer and cardiovascular disease. Table 3 lists specific diseases for which more than 99 percent of the burden falls in low- and middle-income countries, which include malaria, schistosomiasis and leprosy (Lanjouw and Cockburn, 2001).

However, many diseases affect both developed and developing countries. For instance, cancer and heart disease account for 15 percent of the total disease burden even in low- and middle-income countries (Lanjouw, 2001). Moreover, the disease environment in developing countries is projected to become substantially more like that in developed countries over the next 20 years (WHO, 2000).

Weak Health Care Systems and Misuse of Pharmaceuticals

Misuse of pharmaceuticals is a significant problem in developed countries, but it is a much greater problem in many developing countries, where health care systems are often weak and qualified medical personnel are scarce. Whereas the United States has 2.7 trained physicians per thousand people and Europe has 3.9, sub-Saharan Africa has only 0.1 physicians per thousand people (World Bank, 2001b). In some low-income countries, medical personnel assigned to public clinics often do not show up, particularly in rural areas. Moreover, clinics in developing countries often lack drugs because salaries of health care workers take priority in budget allocations and because drug procurement and distribution is inefficient or corrupt.[2]

Many patients therefore rely on the private health care system, but private practitioners are often untrained (Das, 2000). Medical personnel often prescribe inappropriate pharmaceuticals, in part to demonstrate effort to the patient. For instance, in Africa, injections are often given rather than pills, as many patients see these as more powerful. In a detailed study of medication in India, Phadke (1998) categorized more than 50 percent of all drugs prescribed as "unnecessary" or "contra-indicated," although some of these judgments are subjective.

Moreover, while self-prescription is not uncommon in the west, it is extremely common in the poorest countries, where rules requiring prescriptions for pharmaceutical purchases are typically not enforced, perhaps in part because of the shortage of trained physicians (Kamat and Nichter, 1998). Many patients purchase and consume only an incomplete course of medication, especially when symptoms subside after a partial course (Nichter and Nichter, 1996). Drug overuse and misuse speeds the development of drug-resistant forms of diseases because the most resistant parasites are not eliminated, and these resistant parasites are then transmitted to others. For example, chloroquine was once highly effective for preventing and treating malaria, but strains of chloroquine-resistant malaria have emerged in most parts of the world (NIH, 2000). Strains of multidrug-resistant tuberculosis have also emerged over the last decade (NIH, 2000), and the development of resistance to the remaining tuberculosis drugs would pose a severe threat not only to developing countries but also to developed ones.

Pharmaceutical Regulation

Developing countries often simply follow the approval decisions of developed countries rather than conducting their own risk-benefit calculations. While this

[2] See Di Tella and Schargrodsky (2001) on purchases by public hospitals in Argentina.

practice may be appropriate in some cases, it may also block the adoption of needed drugs and vaccines. For example, rotavirus kills three-quarters of a million children each year in developing countries, but it is a minor health nuisance in the United States, causing more than three million cases of childhood diarrhea each year, but few deaths (CVI, 1999; Murphy et al., 2001a). An oral rotavirus vaccine received regulatory approval in the United States and was introduced into the U.S. market in 1998. A few months later, it was withdrawn following evidence that it can cause intususception, a form of intestinal obstruction. Because children in developing countries would have had much greater exposure to disease prior to inoculation, it is not clear that the risk of intususception would be as significant in developing countries. Moreover, even if the risk of intususception were similar, the risk-benefit calculation in countries with high rotavirus mortality would likely overwhelmingly favor vaccine use. The investigators who recommended removing the vaccine from the U.S. market therefore advocated conducting a risk-benefit analysis for the rotavirus vaccine in the developing world (Murphy et al., 2001b).

Yet no such testing and analysis is taking place. There is little hope for profit from selling rotavirus vaccine in the poorest countries, and neither the vaccine developer nor health authorities in developing countries have much incentive to take on the risk of being attacked by activists for conducting trials of a vaccine that is not deemed safe for use in more developed countries. Top-level political leadership from the World Health Organization (WHO) or UNICEF potentially could have provided industry and national authorities with political cover against this risk, perhaps making it feasible for the vaccine developer to give the rights to a nonprofit organization that could conduct testing, but this leadership was not forthcoming.

While following drug approval decisions in the developed countries may sometimes prevent approval of useful drugs, developing countries that depart from this practice can encounter other problems. For instance, the South African government has discouraged the widespread use of Nevirapine, which prevents mother-to-child transmission of AIDS and is an extremely cost-effective intervention, in part because President Mbeki gave credence to discredited scientific theories that HIV does not cause AIDS and that Nevirapine is toxic. (The South African government recently lost a lawsuit that may force the government to allow Nevirapine to be distributed widely, and as of this writing, it appears that the government has conceded and will eventually support the widespread use of Nevirapine.) Kenya and South Africa also each backed several domestically developed but ineffective AIDS drugs. None of these quack remedies provided a cure for AIDS, but they were promoted in part for nationalistic reasons.

Industry Factors

Some of the characteristics of the pharmaceutical industry that differentiate it from other industries are particularly relevant for developing countries. First, the pharmaceutical industry has high fixed R&D costs and low marginal costs of production. Second, the industry is exceptional in that patents rather than first-

mover advantages or other sources of monopoly power provide the key protection for innovators. Third, pharmaceutical regulation and prescription requirements in developed countries facilitate price discrimination across countries by making resale across national borders easier to block. As a result, price differentials between countries are often large.

The chief constraint on further price discrimination is the potential for a political backlash in higher-price markets. Selling pharmaceuticals cheaply in developing countries reveals an upper bound on the marginal cost of production, and developed country politicians and activists may be able to use this information to strengthen their appeals for lower prices. For example, when President Clinton announced his childhood immunization initiative in 1993, he said, "I cannot believe that anyone seriously believes that America should manufacture vaccines for the world, sell them cheaper in foreign countries, and immunize fewer kids as a percentage of the population than any nation in this hemisphere but Bolivia and Haiti" (Mitchell et al., 1993). After a 1982 Congressional hearing in which U.S. Senator Paula Hawkins asked a major vaccine manufacturer how it could justify charging nearly three times as much to the U.S. government for vaccines as to foreign countries, U.S. manufacturers stopped submitting bids to UNICEF to supply vaccines (Mitchell et al., 1993).

Limited Intellectual Property Rights

Many developing countries have historically provided little or no intellectual property rights protection for pharmaceuticals. India, for example, offers patents on pharmaceutical processes but not on products and has developed a large industry that reverse engineers existing drugs. Developed countries, the United States in particular, have pressed developing countries to strengthen protection of intellectual property rights by linking the issue to trade negotiations. The 1994 Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) required the least developed countries to join the rest of WTO member countries in providing 20-year patent protection for pharmaceuticals by 2006 (WTO, 2001a).

However, it is unclear what impact TRIPS will ultimately have on intellectual property rights in developing countries. Several provisions of the agreement provide potential escape hatches. For instance, countries can impose compulsory licensing in national emergencies, the definition of which is deliberately not set out (WTO, 2001a). Countries are still free to impose price controls as well (though firms, of course, are not required to sell to countries with price controls). Moreover, the public storm over pricing of AIDS drugs led WTO negotiators to extend the transition period for instituting patent protection for pharmaceuticals in the least developed countries to 2016 (WTO, 2001b), and it seems possible the deadline could be extended further. Finally, enforcement of WTO provisions relies on countries bringing suits, but as a result of the public outcry, the United States dropped its dispute with South Africa over the country's imports of pharmaceutical products from countries with weaker patent laws and abandoned its dispute with Brazil over generic manufacturing of drugs that are still under patent. It is not clear

whether the WTO will lead to effective intellectual property rights enforcement in developing countries.

Market Failures, Government Failures and Policy Implications

Clearly, the pharmaceutical market in developing countries is rife with market and government failures. Pharmaceutical use is sometimes suboptimal due to pricing above marginal cost and positive treatment externalities for infectious diseases; sometimes too great due to the failure of consumers to take into account externalities from drug resistance; and sometimes simply inappropriate due to information asymmetries between health care providers and their patients. Drug procurement is often inefficient and corrupt, and inappropriate regulation can hinder access. In addition, health care workers are politically powerful relative to patients.

However, the most severe distortions in developing country pharmaceutical markets probably involve dynamic issues. Pharmaceutical firms are reluctant to invest in R&D on the diseases that primarily affect developing countries not only because the poverty of the potential users reduces their willingness to pay, but also because the potential revenue from product sales is far smaller than the sum of customers' potential willingness to pay due to the lack of intellectual property protection and the tendency for governments to force prices down after firms have sunk their research and development costs. The underprovision of R&D on problems facing the poor, even relative to their incomes, implies that a redirection of foreign assistance from private goods, such as food, or even public goods, such as roads, to the international public good of R&D on health problems of the poor could make the poor better-off.

One reason why governments provide suboptimal R&D incentives is that pharmaceutical research and development is a global public good, so each country has an incentive to free ride on research financed by the governments of other countries or induced by their intellectual property rights protection. This is a general problem faced by all countries, not just developing ones. Indeed, the mystery is not why developing countries have historically offered little protection for intellectual property rights, but why small developed countries offer so much. A second reason for suboptimal R&D incentives is that the high fixed costs of R&D and low marginal costs of production for pharmaceuticals create a time-inconsistency problem for governments. Once products have been developed, governments have an incentive to set prices at or near marginal cost. Products are then consumed at the efficient level, and surplus is transferred from (typically foreign) producers to consumers. Governments are in a strong bargaining position because they are major pharmaceutical purchasers, they regulate products and often prices, and they are arbiters of intellectual property rights. However, if pharmaceutical firms anticipate low prices, they will be reluctant to invest. In a repeated game between nations and pharmaceutical producers, this time-inconsistency problem

could potentially be overcome through reputation formation. Indeed, one reason why developed countries are developed may be that these countries were able to establish good reputational equilibria in a variety of areas, including research incentives. Developed countries typically have more stable governments that are more likely to invest in reputation formation for the long run.

Whatever the underlying causes, intellectual property rights for pharmaceuticals in developing countries are weak, and hence the private returns for developing products to fight diseases of developing countries are likely to be a tiny fraction of the social returns to these products. For example, consider a hypothetical future malaria vaccine. A standard way to assess the cost-effectiveness of a health intervention is the cost per Disability Adjusted Life Year saved. A common cost-effectiveness threshold for health interventions in the poorest countries is $100 per DALY. For comparison, health interventions are considered cost-effective in the United States at up to 500 to 1000 times this amount: $50,000–$100,000 per year of life saved (Neumann et al., 2000). At a threshold of $100 per DALY, a malaria vaccine would be cost-effective even at a price of $40 per immunized person (Glennerster and Kremer, 2001), but based on the historical record of vaccine prices, the developer of a malaria vaccine would be lucky to receive payments of one-tenth or one-twentieth of that amount. Of course, a full comparison of the social and private values of a vaccine would also take into account the positive and negative externalities that vaccine development would create for other researchers.

The rest of this article considers a number of public policy issues regarding the availability and use of pharmaceuticals in developing countries from the standpoint of these market and government failures: differential pricing, foreign assistance for health, misuse of pharmaceuticals, drug regulation and procurement and ways of encouraging R&D on products needed by developing countries.

Differential Pricing

Noneconomists often resent price discrimination, but it can improve both access and R&D incentives. Price discrimination allows those who value the product at more than the marginal cost of production to obtain it, so the product reaches more people than under a single worldwide monopoly price. It also allows firms to capture closer to the full social surplus of their products, thus providing them with a greater incentive for product development.

Since the chief constraint on further price discrimination is the fear of undermining prices in developed and middle-income countries, public acknowledgements by politicians in developed countries that different prices are appropriate for different countries could potentially make pharmaceutical firms more willing to risk lowering prices in developing countries. Rich country governments could also facilitate price discrimination by prohibiting imports of pharmaceutical products from countries with weaker patent laws. Individual rich countries can gain by taking advantage of lower-priced imports, but the developed world as a whole is unlikely to benefit, because if developed countries began importing drugs from developing countries on a wider scale, pharmaceutical firms would simply charge

higher prices in developing countries, and their incentives to conduct R&D would be curbed by the smaller total market available to them with lower sales. There is therefore a justification for international agreements to limit such imports since they create negative externalities for other countries. Poor country governments can facilitate price discrimination by taking steps to prevent re-export of pharmaceuticals to rich countries.

However, given that markets in the poorest countries are so small, profit-maximizing prices in poor countries are likely to be substantially above marginal cost if selling at a lower price in these countries has any appreciable effect on prices in rich or even middle-income country markets. Indeed, prices in at least some markets will remain substantially above marginal cost even if governments adopt policies to encourage price discrimination further. Hence, many have called not just for differential pricing in poor countries, but also for using compulsory licensing of patents and/or the threat of compulsory licensing to lower prices closer to marginal cost in poor countries. One potential objection to compulsory licensing is that it could reduce R&D incentives. If restrictions on intellectual property rights were limited to the poorest countries, the impact on research incentives would be minimal for most diseases, but for diseases that primarily affect poor countries, R&D incentives may be affected. Indeed, Lanjouw and Cockburn (2001) find some evidence of a limited reallocation of funds toward malaria research with the introduction of intellectual property concerns into the GATT in the 1990s and the consequent move toward strengthening intellectual property rights protection for pharmaceuticals in developing countries.

Lanjouw (2001) proposes limiting the extension of patent protection in poor countries for pharmaceuticals for global diseases, while allowing patent protection in these countries to increase, as envisaged by the 1994 Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs), on products for diseases that predominately affect the poor. Under her proposal, pharmaceutical developers would effectively have to choose patent protection in either rich or poor countries for a designated list of global diseases, such as cancer. Because developing countries contribute little to the profits firms can realize from pharmaceuticals for global diseases, patent applicants would choose protection in developed countries. Differential patent protection would facilitate beneficial differential pricing. If a firm sold a product for a global disease in a developing country at a high price, other firms could enter the market. (This is essentially equivalent to allowing compulsory licensing for global diseases.)

Lanjouw's (2001) proposal would be fairly close to returning to a pre-TRIPS patent regime for global diseases, but would preserve the limited existing incentives to develop products primarily needed in developing countries, such as a malaria vaccine, because it preserves intellectual property protections in those cases. Moreover, the proposal is robust to errors in the list of global diseases. For example, if all forms of cancer were designated as global diseases, but a form of cancer specific to Africa was later identified, the developer of a drug against this form of cancer could choose patent protection in developing countries. However, since incentives

for R&D on diseases of developing countries are inadequate, new ways of providing incentives for R&D on these products would still be needed.

A potentially difficult problem with limiting intellectual property rights in the poorest countries is the political effects on prices in the middle- and high-income countries. If sanctioning weak or no intellectual property rights in the poorest countries weakened political support for intellectual property rights in richer countries or put pressure on prices there, it could have a significant impact on research incentives for global diseases. If India has limited intellectual property rights, Brazil may not be inclined to provide intellectual property rights either; and if antiretroviral drugs cost $500 per year in Brazil, European governments may lower the prices they pay for the drugs, and U.S. AIDS activists may object to paying $10,000 per year. Moreover, the existence of different intellectual property rights rules in different countries may undermine attempts to cast intellectual property rights protection as a natural, self-evident right rather than as an institution justified by its instrumental value. Of course, it is difficult to predict the political links between pricing in low-, middle- and high-income countries, but the fact that pharmaceutical firms pressed for the TRIPS agreement suggests that they think these links could be significant. If this channel is indeed important, weak intellectual property rights in poor countries could limit R&D incentives.

It may therefore be worth considering an alternative approach in which firms simply donate products to the poorest countries rather than charging the manufacturing cost. This could bolster firms' reputations, rather than posing a public relations challenge in maintaining prices in developed countries. In fact, in the fight over pricing AIDS drugs, antiretroviral producers sought to donate their AIDS drugs in Africa, but activists insisted on countries paying for the drugs at low prices, believing that firms would not continue the donations once the political heat was off.

To give firms an incentive to continue donating their products, developed country governments could provide enhanced tax deductions to pharmaceutical firms that make approved donations of drugs or vaccines for use in developing countries. The U.S. government currently provides a tax deduction for donations, but it is based on the product's manufacturing cost, which is often very low. An enhanced tax deduction or credit could be based on some fraction of a product's U.S. price or on an estimate of the social benefit of the product, perhaps measured in dollars per Disability Adjusted Life Years saved. Such a provision would have to be limited to appropriate donations, requested by approved organizations and shown to be reaching those who need them, or else firms could profit by donating unneeded products with low production costs. This approach would provide the benefits of price discrimination without jeopardizing either research incentives or the principle of intellectual property rights.

Priorities for Foreign Assistance in Health

The World Health Organization's Commission on Macroeconomics and Health (CMH), chaired by economist Jeffrey Sachs, has called for developed

countries to increase assistance for health in the developing world by $27 billion annually by 2007 and $38 billion annually by 2015 (CMH, 2001). A significant share of this would be for pharmaceuticals, including antiretroviral treatments for AIDS.

The Commission report argues that these investments in health will pay for themselves six times over through higher productivity and increased earnings (CMH, 2001). However, evidence on the magnitude of the economic impact of health gains is patchy. Extravagant claims based on cross-country regressions should be taken with a grain of salt in light of the poor economic performance of Africa from the 1960s through the 1990s, despite the substantial technology-driven improvements in health over the period, and by the more recent stellar growth performance of Uganda, one of the countries earliest and hardest hit by AIDS morbidity and mortality. In my view, a stronger case for health spending rests on its effect on welfare rather than measured GDP. Indeed, the 13 percent decline in official GDP in the low-income countries of sub-Saharan Africa from 1972 to 1992 while life expectancy increased by nearly 10 percent and infant mortality fell 30 percent suggests that measured GDP can in some cases be a poor guide to welfare. A version of GDP that was corrected to measure improvements in the productivity of health services over this period would probably not have declined over the period.

Economists have advocated two main approaches for determining priorities for the limited foreign assistance that is likely to be forthcoming for health from the developed world. Some argue that the interventions that save the greatest number of lives at the least cost should be prioritized, using cost per Disability Adjusted Life Years saved as a guideline. Others argue that outside assistance should concentrate on addressing market failures, for example by funding public goods. However, the debate between advocates of the cost-effectiveness and market failure approaches may be overblown. To the extent that analysts estimate DALYs correctly and consumers value DALYs incurred by different diseases equally (rather than being willing to pay more to avoid deaths from airplane crashes than automobile accidents, for example), the two approaches should yield broadly similar results. Indeed, they do point to similar health priorities. For example, the WHO Expanded Program on Immunization is extremely cost-effective, at only around $20 to $40 per DALY saved, in part because vaccination creates positive externalities by preventing the spread of disease. Treatments for some infectious diseases would likely be another priority under both approaches. For example, school-based mass treatment of intestinal worm infections would cost as little as $7 per DALY saved, and the externality benefits of such treatments can account for over 70 percent of the reduction in disease burden (Miguel and Kremer, 2002). Some AIDS interventions are also very cost-effective. Nevirapine is extremely cost-effective in preventing mother-to-child transmission of AIDS, at $5 to $20 per DALY saved (Marseille et al., 1999), and a targeted AIDS prevention program in Tanzania costs an estimated $10 to $12 per DALY saved (World Bank, 1999).

Given a fixed budget, helping extend the programs above to reach more people is likely to be a much higher priority than using antiretroviral drugs to treat

HIV/AIDS. The well-known call by 133 Harvard faculty members for antiretroviral treatment in developing countries estimates that, even given the recent dramatic reductions in prices by pharmaceutical firms, purchasing and delivering antiretrovirals will cost $1,100 per person per year (Adams et al., 2001). This is in large part because the drugs are so difficult to deliver safely and effectively. Because the drugs cause significant side effects and must be taken according to a rigid schedule if they are to be effective and not lead to the spread of drug resistance, they require monitoring by medical personnel. Adherence to drug regimes is highly imperfect even in rich countries with good medical care (Ammassari et al. 2001; Brook et al., 2001; Nieuwkerk et al., 2001). The statement by the 133 Harvard faculty members therefore advocates "directly observed therapy," wherein a community health worker visits each patient and observes him or her taking the antiretroviral medication. It is worth noting, however, that recent randomized controlled trials find that direct observation is no more effective than self-administered treatment for tuberculosis (Walley et al., 2001). But even setting this issue aside, many more lives could be saved with alternative interventions given the $1,100 per patient per year estimated cost of antiretroviral therapy. For instance, for every person treated for a year with antiretroviral therapy, 25 to 110 Disability Adjusted Life Years could be saved through targeted AIDS prevention efforts or vaccination against easily preventable diseases.

Advocates of antiretroviral drugs for HIV/AIDS often argue that treatment encourages prevention and slows transmission, since people do not have incentives to be tested unless treatment is available. However, the impact of antiretrovirals on the spread of the AIDS epidemic is unclear. Even if the availability of treatment encourages testing, knowledge of HIV status may not prevent the spread of the disease, since people who are infected may decide they have nothing left to lose. Moreover, while treatment with antiretroviral therapy may lower viral loads and reduce transmission, it may also help HIV-infected people stay sexually active longer, contributing to the spread of the disease. Finally, the expectation of treatment could reduce incentives to adopt safer behaviors. While there is no clear theoretical presumption about the effect of subsidizing antiretroviral therapies on the rate of transmission of HIV in low-income countries, there is at least some empirical evidence that the availability of treatment has led to a resurgence of risky behavior in the United States (Lehman et al., 2000). There is also anecdotal evidence that risky sexual behavior increased in Kenya following fraudulent announcements of an AIDS cure (McGreal, 1996).

Some advocates of antiretroviral treatment argue that public campaigns to extend antiretroviral treatment will generate enough new aid that both antiretrovirals and other interventions can be funded. It is worth bearing in mind, however, that even if 90 percent of funds for antiretroviral therapy were "new" foreign aid, and only 10 percent were diverted from vaccination efforts, more lives would be lost from reductions in vaccinations than would be gained through antiretroviral therapy. Calls for foreign assistance to provide antiretroviral therapy might thus

stipulate that any available funds should be used in the way that saves the most lives, so that if only a small amount was provided, it would be used to cover low-cost interventions such as vaccinations, but that if a larger amount was made available, it could be used to cover antiretroviral therapy.

Since individual countries can potentially correct market failures within their borders, it may make sense to focus foreign assistance on the provision of global public goods. Key global public goods include slowing the development of drug resistance, creating knowledge on drug efficacy and safety, and, most important, R&D on new pharmaceuticals. Since the spread of a disease once it crosses national borders is determined primarily by conditions within the host nation, cross-border externalities from improved disease control are likely to be small, with the exception of diseases near eradication, such as smallpox in the 1970s and polio now.

Addressing Misuse of Pharmaceuticals

Since misuse of pharmaceuticals that facilitates the development of drug resistance creates negative externalities for the rest of the world, discouraging drug misuse is a global public good. However, the impact of pharmaceutical prices on externalities from drug resistance is ambiguous. Higher prices could reduce the number of people taking drugs and thus reduce the spread of drug resistance, but higher prices could also lead those people who do take the drug to take incomplete doses, promoting the spread of drug resistance. The latter effect may be particularly likely in developing countries, where pharmaceuticals are often taken with weak medical supervision. Conceivably, governments could require medicines to be packaged for sale only in complete courses and could penalize stores selling fractions of a course. However, shopkeepers in developing countries routinely sell individual units from packages, and monitoring this would be difficult. Another possibility would be to subsidize combination therapies that are less likely to induce drug resistance.[3]

Improving the overall quality of medical care would also reduce the spread of drug resistance by helping to ensure that pharmaceuticals are used appropriately and that patients are encouraged to complete the course of treatment. Branding and franchising of medical practices and care facilities could potentially help address the problems of asymmetric information between patients and providers. Mission hospitals in Africa have managed to develop reputations for providing quality care, for example (Leonard, 2002). Managing such branding efforts could be difficult, however, and the effectiveness of such efforts is uncertain. In some countries, the Internet might potentially play a role in facilitating the standardization of medical care. Clinic workers with only moderate levels of training could enter patient information, and programs on the Internet could offer possible

[3] For example, Mead Over has suggested that subsidizing combination therapies for AIDS might reduce the risk of drug resistance developing since while this practice would encourage greater use of multidrug therapy, it might discourage the use of monotherapies that are more prone to drug resistance.

diagnoses for them to consider as well as advice on when referrals are needed. Such a system could complement the services currently provided by health care workers and help to monitor whether local health care workers were showing up to work or were likely to be routinely mistreating patients. Efforts to experiment with such approaches deserve international support since they could potentially lead to innovations in health care delivery that would be beneficial across much of the developing world.

R&D on Needed Products

As discussed earlier, current incentives for the development of products needed primarily by developing countries are inadequate. Vaccines for malaria, tuberculosis and the strains of AIDS prevalent in Africa are a prime example. Programs to encourage R&D can take two broad forms. "Push" programs subsidize research inputs—for example, through grants to researchers or R&D tax credits. "Pull" programs reward research outputs, for example, by committing in advance to purchase a specified amount of a desired product at a specified price. Both approaches have important roles, but current policy underutilizes pull programs.

Push programs are subject to asymmetric information between researchers and program administrators and between these groups and politicians and the public, giving rise to both moral hazard and adverse selection. Moral hazard arises because funders cannot perfectly monitor the actions of grant recipients, and grant recipients may have incentives to devote effort to pursuing general scientific research or preparing their next grant application rather than focusing on development of the desired product. In contrast, under a pull program, researchers will not receive payment unless a useable product is delivered, so researchers have incentives to focus on developing the desired product.

Adverse selection arises because researchers have more information than do funders about the probability that their research will lead to successful products. Research administrators and their ultimate employers—elected officials and the general public—may not be able to determine which research projects in response to certain diseases are worth pursuing, nor which diseases and products should be targeted. Decision makers may therefore wind up financing ideas with only a minute probability of success, or worse, failing to fund promising research because they do not have confidence that its backers are presenting objective information on its prospects. In contrast, under a pull program in which developers are rewarded only if they successfully produce the desired product, there is a strong incentive for firms considering research investments to assess the prospects for success realistically.

The moral hazard and adverse selection problems that plague push programs are illustrated by the U.S. Agency for International Development's (USAID) 1980s program to develop a malaria vaccine. During the USAID program, external evaluators suggested that additional funding should not be provided to two of the three research teams. However, as a result of information provided by the project director, USAID provided substantial new resources to all three teams and was

sufficiently confident that vaccines would be developed that it even arranged to purchase monkeys for testing a vaccine. Two of three researchers diverted grant funds into their private accounts and were later indicted for theft and criminal conspiracy. The project director received kickbacks from the contract to purchase monkeys and eventually pleaded guilty to accepting an illegal gratuity, filing false tax returns and making false statements. In 1984, before the indictments, 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" (Desowitz, 1991). By the end of the project, USAID had spent $60 million on its malaria vaccine effort with few results. While the example is extreme, it vividly illustrates the problems with push programs.

As an alternative to direct government financing of research, some have proposed R&D tax credits targeted to private research on drugs and vaccines needed by developing countries. However, such tax credits are subject to similar problems. Firms would have an incentive to relabel as much of their R&D as possible as eligible for the targeted credit. For example, if there were an R&D tax credit for a malaria vaccine, researchers might focus on a vaccine that would likely only provide temporary protection and would be suitable for travelers and military personnel spending only short times in developing countries, but not for residents of these areas. To take another example, modern vaccines typically include both antigens specific to a particular organism and adjuvants that potentially boost the effectiveness of several different vaccines. Firms would have every incentive to claim that an adjuvant intended for an ineligible vaccine was actually for a malaria vaccine, so as to claim a tax credit. Finally, R&D tax credits will not improve access to products once they are developed.

In contrast, under pull programs, the public pays nothing unless a viable product is developed. Pull programs give researchers incentives to self-select projects with a reasonable chance of yielding a viable product and to focus on developing a marketable product. Under pull programs, governments do not need to "pick winners" among R&D proposals—they simply need to decide what success would be worth to society and offer a corresponding reward. Moreover, appropriately designed pull programs can help ensure that if new products are developed, they will reach those who need them. One kind of pull program is a purchase commitment in which sponsors would commit to purchase a specified number of doses at a specified price if a vaccine meeting certain specifications were developed. Purchase commitment programs are discussed in Kremer (2001a, b), World Bank (1999) and Batson and Ainsworth (2001), while shorter treatments of the idea in the popular press appear in Kremer and Sachs (1999) and Sachs (1999).[4] An example of a purchase commitment would be for developed countries or private

[4] An alternative push program design that has been proposed is to reward developers with extensions of patents on other pharmaceuticals. This would inefficiently and inequitably place the entire burden of financing development on patients who need these other pharmaceuticals. For example, giving a patent

foundations to commit to purchase malaria vaccine at $5 per immunized person and to make it available to developing countries either free or for a modest copayment.

A key limitation of pull programs is that they require specifying the output in advance. A pull program could not have been used to encourage the development of the Post-It Note® or the graphical user interface, because these products could not have been adequately described before they were invented. Similarly, pull programs may not work well to encourage basic research, because it is typically difficult to specify the desired results of basic research in advance. (Of course, some basic research outputs, such as proving Fermat's last theorem, can be defined in advance.) Simply rewarding the development of applied products is not a good way to stimulate basic research, since a program that tied rewards to the development of a specific product would encourage researchers to keep their results private as long as possible to have an advantage in the next stage of research. Indeed, a key objective of basic research is to provide information to other researchers, rather than to develop products, and grant-funded academics and scientists in government laboratories have career incentives to publish their results quickly. In contrast to unanticipated inventions, like the Post-It Note®, or to basic research, it is comparatively easier to define what is meant by a safe and efficacious vaccine, especially as existing institutions, such as the U.S. Food and Drug Administration (FDA), are already charged with making these determinations.

Nonetheless, if donor governments, international organizations or private foundations commit to purchase a future vaccine, the eligibility rules they set will be key. Eligibility conditions for candidate products would likely include some minimal technical requirements. These technical requirements could include clearance by a regulatory agency, such as the U.S. FDA, or a waiver of regulatory approval in developed countries for products that would pass a risk-benefit analysis for use in developing, but not developed, countries. Products that pass these requirements might then be subject to a market test: nations wishing to purchase products might be required to provide a modest copayment tied to their per capita income, so that countries would have an incentive to investigate carefully whether candidate products are appropriate for their local conditions. This provision would also help to assure that limited donor funds are allocated well and would increase incentives for developers by increasing the payment offered to the successful developer. On the other hand, it could reduce the confidence of potential vaccine developers in the program. A purchase commitment could also include a system of bonus payments for products that exceed the minimum requirements. Eligibility conditions should also specify who will have authority to judge whether the eligi-

---

extension on Prozac for developing an HIV vaccine could prevent some people from getting needed treatment for depression.

bility conditions have been fulfilled. Ideally, these adjudicators should be insulated from political pressure through long terms of service.

A well-written contract should also be credible to potential vaccine developers. Courts have held that similar public commitments to reward contest winners or to purchase specified goods constitute legally binding contracts and that the decisions of independent parties appointed in advance to adjudicate such programs are binding. For example, in the 1960s, the U.S. government pledged to purchase, at a minimum price, domestically produced manganese. After the world price of the commodity fell, the General Services Administration (GSA), the U.S. agency in charge of administering the program, attempted to renege, but U.S. courts forced the GSA to honor the commitment (Morantz and Sloane, 2001).

The total market promised by a purchase commitment should be large enough to induce substantial effort by vaccine developers, but less than the social value of the vaccine. The larger the market for a product, the more firms will enter the field, the more research leads each firm will pursue, and the faster a product will be developed. Given the enormous burden of diseases such as malaria, tuberculosis, and HIV/AIDS, it is important to provide sufficient incentive for many researchers to enter the field and to induce major pharmaceutical firms to pursue several potential leads simultaneously so that products can be developed quickly. There is little risk that payments made as a result of a purchase commitment could exceed the cost of saving the equivalent number of lives using today's treatments.

Prior work by the author and others suggests that an annual market of $250 million to $500 million is needed to motivate substantial research (Kettler, 1999; Kremer, 2001b; Mercer Management Consulting, 1998). A commitment at this level to purchase vaccines for malaria, tuberculosis and HIV/AIDS would be extremely cost effective, costing nothing if a useable product was not developed and as little as $4 per year of life saved if a vaccine were developed.

Purchase commitments could potentially be implemented by national governments, international organizations, or private foundations. A number of policymakers have indicated interest in this approach. As U.S. Treasury Secretary, Lawrence Summers advocated a closely related tax credit for sales of vaccines, where every dollar of qualifying vaccine sales to nonprofit and international organizations serving developing countries would be matched by a dollar of tax credit, effectively doubling the incentive to develop vaccines for neglected diseases. This proposal was part of the Clinton administration's FY 2001 budget, but did not become law. Senators William Frist (R-TN) and John Kerry (D-MA) and Representatives Nancy Pelosi (D-CA) and Jennifer Dunn (R-WA) have proposed both the tax measure and a purchase commitment in the Vaccines for the New Millennium Act.

The purchase commitment approach has also attracted interest from policymakers internationally, including the United Kingdom's Chancellor of the Exchequer, the United Kingdom Cabinet Office, the German foreign minister, and the Dutch development minister (Brown, 2001; Elliott and Atkinson, 2001; PIU, 2001). The World Bank president, James Wolfensohn, has said that the institution plans to

create a $1 billion fund to help countries purchase specified vaccines if and when they are developed ("Discovering Medicines for the Poor," 2000). However, the World Bank has yet to act on this commitment. The Gates Foundation, with $22 billion in assets and a focus on children's health in developing countries and vaccines in particular, is also well-placed to forward a vaccine purchase commitment. While continuing to fund its other priorities, such a foundation could simply pledge that if a product were actually developed, the foundation would purchase and distribute it in developing countries.

Drug Regulation and Procurement

The case of rotavirus vaccine suggests that if developing countries simply rely on regulatory institutions in developed countries, decisions will not always be appropriate given the different benefit-cost ratios for particular pharmaceuticals in developing countries. On the other hand, the Kenyan and South African governments' endorsement of ineffective but domestically developed AIDS "cures" suggests that if individual developing countries without adequate domestic institutions make regulatory decisions, decisions may reflect politics and nationalism as much as health concerns. Since gathering information on drug safety and efficacy is an international public good, there may be a role for an international body to review developed country pharmaceutical approval decisions for relevance to developing country conditions and, where appropriate, to sponsor additional trials or issue alternative certification. The organization could make a recommendation on the appropriateness of the product for use in different circumstances, and each country could then decide whether to follow that recommendation. However, the World Health Organization has historically eschewed such a role, and it is not clear that it is equipped to act as a regulatory body. Like many other international organizations, the quality of WHO's work sometimes suffers as member countries invest resources in seeking funding, contracts, or leadership positions rather than in trying to improve the organization as a whole.[5]

Milton Friedman (Friedman and Friedman, 1980) has suggested replacing pharmaceutical regulation and prescription requirements with a system of mandatory labeling and letting consumers make their own decisions on pharmaceutical use. While proponents of strict drug regulation point to disasters of premature approval, such as thalidomide, opponents argue that the health burden of regulatory delays in approving new drugs far exceeds the health costs of these well-publicized disasters. It seems possible, for example, that the failure to proceed with the rotavirus vaccine in developing countries will cost millions of lives.

In my view, the justification for pharmaceutical regulation needs to be reconceptualized. Were the declared purpose of pharmaceutical regulation—to protect current consumers from unsafe and ineffective drugs—the main reason for regu-

[5] For instance, in 1993, Hiroshi Nakajima was re-elected to head WHO amid allegations that Japan bribed developing nations to vote for the Japanese Director General (Crossette, 1998).

lation, Friedman's (Friedman and Friedman, 1980) proposal would be appealing. I would argue, however, that the primary advantage of drug regulation is that it creates incentives for firms to conduct the randomized trials that provide information on product effectiveness for future consumers. The current regulatory system, in which products that have not undergone clinical trials cannot be sold legally, gives pharmaceutical firms an incentive to conduct these trials and to do so in a rigorous enough manner to pass muster with regulators. If new pharmaceuticals were available during trials, it may be difficult to preserve the integrity of the comparison group necessary for conducting randomized trials. Seen in this light, drug regulation denies current consumers the option of taking unproven drugs, but it provides future consumers with information about the drugs.

Since incentives from large rich country markets are sufficient to encourage testing, small poor countries may want to consider requiring labels that tell customers whether the product received regulatory approval, but not prohibiting sales of products for which approval had not been granted. On the other hand, the traditional justification for drug regulation may better apply in environments where consumers are often illiterate, deceptive advertising is difficult to regulate and tort law is weak. In such environments, replacing prohibition with labeling could potentially exacerbate misuse of pharmaceuticals. The best case for replacing drug regulation with labeling requirements could therefore be made in small developed countries, such as Australia or New Zealand.

Some have proposed posting information on all public pharmaceutical purchases on the Internet as a way to improve pharmaceutical procurement by developing country governments, and such a system has been tried in Brazil. This system has been advocated as a way to provide information to ill-informed public purchasers and strengthen their bargaining power, but posting prices could also facilitate collusion among suppliers to keep prices high. A better rationale for the system is that publicly posting prices could help reduce corruption in drug procurement, which is likely a bigger problem than collusion by sellers.

Conclusions

Pharmaceuticals have brought tremendous health improvements to developing countries. The international community could greatly increase these benefits by implementing systems to provide better access to existing pharmaceuticals and to manage their use, as well as by investing in the global public good of R&D on diseases that disproportionately affect the poor. Developing countries could redirect their health budgets away from salaries and toward cost-effective public health measures, such as vaccination and school-based control of intestinal worms, and could explore institutional reforms for health care delivery. Developed countries and international organizations could encourage differential pricing, allow more favorable tax treatment of appropriate drug donations, and encourage R&D and

facilitate access to new products by committing in advance to purchase products needed in developing countries if and when they are developed.

■ *I am grateful to Jessica Leino for outstanding research assistance and to Ernst Berndt, Jishnu Das, Brad De Long, Varun Gauri, Dean Jamison, Lynn Johnson, Jenny Lanjouw, Mead Over, Timothy Taylor, Michael Waldman and David Webber for suggestions.*

References

Adams, Gregor et al. 2001. "Consensus Statement on Antiretroviral Treatment for AIDS in Poor Countries." Available at ⟨http://www.hsph.harvard.edu/organizations/hai/overview/news_events/events/consensus.html⟩.

Ammassari, Adriana et al. 2001. "Self-Reported Symptoms and Medication Side Effects Influence Adherence to Highly Active Antiretroviral Therapy in Persons with HIV Infection." *Journal of Acquired Immune Deficiency Syndromes.* December 15, 28:5, pp. 445–49.

Attaran, Amir and Lee Gillespie-White. 2001. "Do Patents for Antiretroviral Drugs Constrain Access to AIDS Treatment in Africa?" *Journal of the American Medical Association.* October 17, 286: 15, pp. 1886–892.

Balke, Nathan S. and Robert J. Gordon. 1989. "The Estimation of Prewar Gross National Product: Methodology and New Evidence." *Journal of Political Economy.* February, 97, pp. 38–92.

Batson, Amie and Martha Ainsworth. 2001. "Private Investment in AIDS Vaccine Development: Obstacles and Solutions." *Bulletin of the World Health Organization.* 79:8, pp. 721–27.

Brook, M.G. et al. 2001. "Adherence to Highly Active Antiretroviral Therapy in the Real World: Experience of Twelve English HIV Units." *AIDS Patient Care STDS.* September, 15:9, pp. 491–94.

Brown, Gordon. 2001. Speech given by Gordon Brown, Chancellor of the Exchequer, at the International Conference Against Child Poverty, London, February 26. Available at ⟨http://www.hm-treasury.gov.uk/docs/2001/child_povesrty/chxspeech.htm⟩.

CMH (Commission on Macroeconomics and Health). 2001. "Macroeconomics and Health: Investing for Health." Available at ⟨http://www.cid.harvard.edu/cidcmh/CMHReport.pdf⟩.

Costa, Dora. 2001. "Estimating Real Income in the United States from 1988 to 1994: Correcting CPI Bias Using Engel Curves." *Journal of Political Economy.* December, 109:6, pp. 1288–310.

Crossette, Barbara. 1998. "At W.H.O., 2 Physicians Lead the Race for Top Job." *New York Times.* January 11, Section 1, p. 4.

CVI (Children's Vaccine Initiative). 1999. CVI Forum No. 16. Geneva.

Das, Jishnu. 2000. "Do Patients Learn About Doctor Quality?: Theory and an Application to India." Manuscript, Harvard.

Desowitz, Robert S. 1991. *The Malaria Capers: Tales of Parasites and People.* New York: W. W. Norton.

Di Tella, Rafael and Ernesto Schargrodsky. 2001. "The Role of Wages and Auditing during a Crackdown on Corruption in the City of Buenos Aires." Manuscript, Harvard.

Elliott, Larry and Mark Atkinson. 2001. "Fund to Beat Third World Disease." *Guardian.* February 23. Available at ⟨http://www.guardian.co.uk/international/story/0,3604,441835,00.html⟩.

"Discovering Medicines for the Poor." 2000. *Financial Times.* February 2, p. 7.

Fogel, Robert W. 1986. "Nutrition and the Decline in Mortality Since 1700: Some Preliminary Findings," in *Long-Term Factors in American Economic Growth.* Stanley L. Engerman and Robert E. Gallman, eds. Chicago: University of Chicago Press, pp. 439–527.

Friedman, Milton and Rose Friedman. 1980. *Free to Choose.* New York: Harcourt Brace Jovanovich.

Glennerster, Rachel and Michael Kremer. 2001. "A Vaccine Purchase Commitment: Cost-Effectiveness Estimates and Pricing Guidelines." Unpublished Manuscript.

Jamison, Dean T. et al. 2001. "Cross-Country Variation in Mortality Decline, 1962–87: The Role of Country-Specific Technical Progress." CMH Working Paper No. WG1:4, April.

Johnston, Louis and Samuel H. Williamson. 2002. "The Annual Real and Nominal GDP for the United States, 1789–Present." Economic History Services, April, available at ⟨http://www.eh.net/hmit/gdp/⟩.

Kamat, Vinay R. and Mark Nichter. 1998. "Pharmacies, Self-Medication and Pharmaceutical Marketing in Bombay, India." *Social Science and Medicine.* 47:6, pp. 779–94.

Kettler, Hannah E. 1999. "Updating the Cost of a New Chemical Entity." London, Office of Health Economics.

Kim-Farley, R. and the Expanded Programme on Immunization Team. 1992. "Global Immunization." *Annual Review of Public Health.* 13, pp. 223–37.

Kremer, Michael. 2001a. "Creating Markets for New Vaccines: Part I: Rationale," in *Innovation Policy and the Economy.* Adam B. Jaffe, Josh Lerner, and Scott Stern, eds. Cambride: MIT Press, pp. 35–72.

Kremer, Michael. 2001b. "Creating Markets for New Vaccines: Part II: Design Issues," in *Innovation Policy and the Economy.* Adam B. Jaffe, Josh Lerner, and Scott Stern, eds. Cambride: MIT Press, pp. 73–118.

Kremer, Michael and Jeffrey Sachs. 1999. "A Cure for Indifference." *Financial Times.* May 5, available at ⟨http://www.brook.edu/views/oped/kremer/19990505.htm⟩.

Kurian, George Thomas. 1994. *Datapedia of the United States 1790–2000.* Lanham, Md.: Bernan Press.

Lanjouw, Jean O. 2001. "A Patent Policy Proposal for Global Diseases." Brookings Policy Brief, June.

Lanjouw, Jean O. and Iain M. Cockburn. 2001. "New Pills for Poor People? Empirical Evidence after GATT." *World Development.* 29:2, pp. 265–89.

Lehman, Stan et al. 2000. "Are At-Risk Populations Less Concerned about HIV Infection in the HAART Era?" San Francisco, CDC Seventh Conference on Retroviruses and Opportunistic Infections, January 30–February 2.

Leonard, Kenneth L. 2002. "When Both States and Markets Fail: Asymmetric Information and the Role of NGOs in African Health Care." *International Review of Law and Economics.* July, 22:1, pp. 61–81.

Marseille, E. et al. 1999. "Cost-Effectiveness of Single-Dose Nevirapine Regimen for Mothers and Babies to Decrease Vertical HIV-1 Transmission in Sub-Saharan Africa." *Lancet.* September 4, 354:9181, pp. 803–09.

McGreal, Chris. 1996. "Horror Greets AIDS 'Miracle Cure.'" *Guardian.* May 25, p. 11.

Mercer Management Consulting. 1998. "HIV Vaccine Industry Study October-December 1998." World Bank Task Force on Accelerating the Development of an HIV/AIDS Vaccine for Developing Countries.

Miguel, Edward and Michael Kremer. 2002. "Worms: Education and Health Externalities in Kenya." Manuscript, Harvard.

Mitchell, Violaine S. et al. 1993. *The Children's Vaccine Initiative: Achieving the Vision.* Washington, D.C.: National Academy Press.

Morantz, Alison and Robert Sloane. 2001. "Vaccine Purchase Commitment Contract: Legal Strategies for Ensuring Enforceability." Mimeo, Harvard University.

Murphy, Trudy V. et al. 2001a. "Intussusception Among Infants Given an Oral Rotavirus Vaccine." *New England Journal of Medicine.* February 22, 344:8, pp. 564–72.

Murphy, Trudy V. et al. 2001b. "Intussusception and an Oral Rotavirus Vaccine." *New England Journal of Medicine.* June 14, 344:24, pp. 1866–867.

Murray, Christopher J. L. and Alan D. Lopez. 1996. *The Global Burden of Disease: a Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020. Global Burden of Disease and Injury Series, Volume 1.* Cambridge, Mass.: Published by the Harvard School of Public Health on behalf of the World Health Organization and the World Bank, Distributed by Harvard University Press.

Neumann, Peter J. et al. 2000. "Are Pharmaceuticals Cost-Effective? A Review of the Evidence." *Health Affairs.* March/April. 19:2, pp. 92–109.

Nichter, Mark and Mimi Nichter. 1996. *Anthropology and International Health: Asian Case Studies.* Amsterdam: Gordon and Breach.

Nieuwkerk, P.T. et al. 2001. "Limited Patient Adherence to Highly Active Antiretroviral Therapy for HIV-1 Infection in an Observational Cohort Study." *Archives of Internal Medicine.* September 10, 161:16, pp. 1962–968.

NIH (National Institutes of Health). 2000. "Fact Sheet: Antimicrobial Resistance." Available at ⟨http://www.niaid.nih.gov/factsheets/antimicro.htm/⟩, June.

Pecoul, Bernard et al. 1999. "Access to Essential Drugs in Poor Countries: A Lost Battle?" *Journal of the American Medical Association.* January 27, 281:4, pp. 361–67.

Phadke, Anant. 1998. *Drug Supply and Use: To-*

wards a Rational Policy in India. New Delhi: Sage Publications.

PhRMA. 2000. *PhRMA Industry Profile 2000.* Available at ⟨http://www.phrma.org/publications/publications/profile00/⟩.

PIU (Performance and Innovation Unit, Cabinet Office). 2001. "Tackling the Diseases of Poverty: Meeting the Okinawa/Millenium Targets for HIV/AIDS, Tuberculosis, and Malaria." London, May 8. Available at ⟨http://www.cabinet-office.gov.uk/innovation/healthreport/default.htm⟩.

Preston, Samuel H. 1975. "The Changing Relation between Mortality and Level of Economic Development." *Population Studies.* July, 29:2, pp. 231–48.

Sachs, Jeffrey. 1999. "Helping the World's Poorest." *Economist.* August 14, 352:8132, pp. 17–20.

United States Census. 2000. Available at ⟨http://www.census.gov/dmd/www/2khome.htm⟩.

Walley, John D. et al. 2001. "Effectiveness of the Direct Observation Component of DOTS for Tuberculosis: A Randomised Controlled Trial in Pakistan." *Lancet.* March 3, 357, pp. 664–69.

WHO (World Health Organization). 1996. *Investing in Health Research and Development: Report of the Ad Hoc Committee on Health Research Relating to Future Intervention Options.* Geneva: WHO.

WHO (World Health Organization). 2000. *World Heath Report 2000.* Geneva: WHO.

WHO (World Health Organization). 2001. *World Heath Report 2001.* Geneva: WHO.

World Bank. 1999. *Confronting AIDS: Public Priorities in a Global Epidemic.* Washington, D.C.: Oxford University Press.

World Bank. 2001a. *Immunization at a Glance.* Washington, D.C.: World Bank, November.

World Bank. 2001b. *World Development Indicators.* Washington, D.C.: Oxford University Press.

WTO. 2001a. "Fact Sheet: TRIPS and Pharmaceutical Patents." April.

WTO. 2001b. "Declaration on the TRIPS Agreement and Public Health." Available at ⟨http://www-chil.wto-ministerial.org/english/thewto_e/minist_e/min01_e/min01_14nov_e.htm⟩.