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We need to
invest more
in vaccines

Chapter at a glance

- Vaccines represent the best hope for large, rapid and affordable improvements in health in the developing world.
- Vaccines developed for affluent countries have already contributed greatly to improving the health of people in poor countries. A remarkable 75% of children receive a basic set of childhood immunizations. But because of shortcomings in financing and delivery, including delays in introduction of life-saving vaccines, more than 3 million people die each year of vaccine-preventable diseases.
- Increasingly, the main diseases in poor countries are not a high priority in affluent countries. As a result, developing countries can no longer depend on rich markets to meet the costs of the development of new vaccines that would benefit poor countries.
- The total market size for vaccines in developing countries is tiny—about \$500 million a year. This is insufficient to provide an incentive for pharmaceutical companies to invest in developing new vaccines for these diseases.
- In addition to being small, the vaccine market is characterized by collective procurement. Success in stretching health budgets by keeping prices as low as possible has important short-term benefits. But the aim of minimizing short-term costs to ensure access must be balanced with the goal of providing returns sufficient to stimulate development of new products.
- Largely as a result of the low value and high risks of the developing country market, less than 10% of global spending on health research and development is devoted to the major health problems of 90% of the population.
- Without a valuable market to stimulate the development of new vaccines for diseases that occur mainly in developing countries, alternative arrangements are needed to ensure that vaccines are developed, produced on a large scale and made available affordably and reliably to developing countries.

Vaccines are important for global health

The importance of the development of new vaccines for the most significant health problems in the developing world can hardly be overstated. Well known as being among the most cost-effective health interventions, immunization can be cost-saving, by preventing diseases that would otherwise require expensive treatment. In general, vaccines are well suited to the needs of developing countries. They are a cheap way to save lives, requiring no costly screening, diagnosis or follow-up.

Extraordinary scientific progress, coupled with effective delivery strategies, has transformed health conditions in the past 50 years, in both rich and poor countries. In the industrial world, for example, basic childhood immunization has almost eliminated many diseases that once crippled, severely sickened or killed thousands of young children each year (figure 1.1).¹

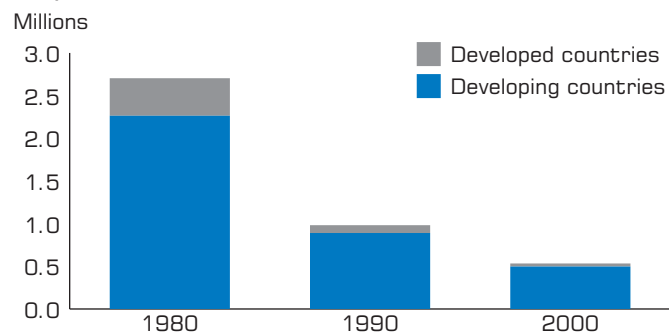
Those same vaccines—originally developed for the United States and Europe—have been used in the developing world, typically sold at low prices after manufacturing capacity had expanded. These low prices are possible because the developers of the vaccines have been able to earn a return on their investment from sales in affluent countries. As patent protection has come to an end, and the markets have become contestable, production volumes have increased and the prices charged to developing countries have fallen close to the marginal cost of production, a few cents. For example, the combined diphtheria, tetanus and pertussis (DTP) vaccine costs about \$0.09 a dose, and the measles vaccine costs about \$0.14 a dose.

Even with lower levels of coverage than in developed countries, these products have had an enormous health impact in the developing world. More than three-quarters of the world's children receive the basic childhood immunizations.

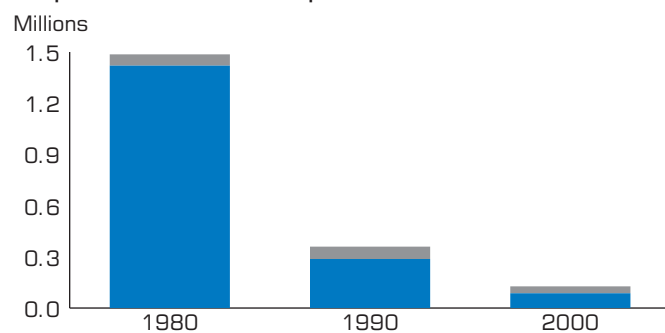
Vaccines have transformed global health. Smallpox used to kill 5 million people a year; thanks to the world's first vaccine, it was eradicated in 1979 (box 1.1). Fifty years ago, polio was the leading cause of paralysis, crippling thousands of children and adults. The eradication of polio through vaccination is tantalizingly close, though it will require continuing focus and commitment from policymakers. Two-thirds of developing countries have eliminated neonatal tetanus. In one year alone (from June 2001) mass measles campaigns in eight African countries vaccinated more than 20 million children and prevented more than 140,000 deaths; measles vaccinations are now preventing 250,000 deaths

Figure 1.1
Basic childhood immunizations reduce reported cases of disease in developed and developing countries—selected examples

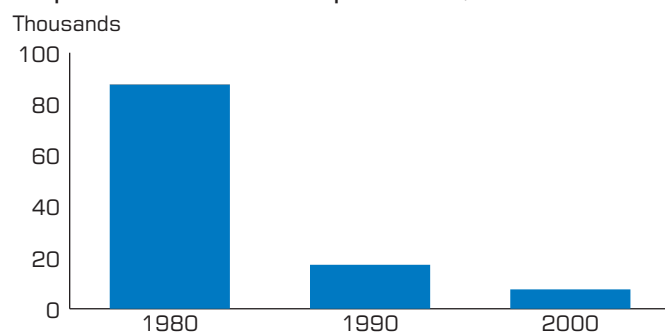
Reported cases of measles, 1980–2000



Reported cases of pertussis, 1980–2000



Reported cases of diphtheria, 1980–2000



Source: WHO Immunization Profiles for Developed and Developing country groups.

a year.² As a result of both routine immunization programs and campaigns, millions of lives are saved every year; and millions more are protected from disease and disability.

Millions die of vaccine-preventable diseases

In many ways, it is extraordinary how effectively vaccines reach children all over the world. More than three-quarters of the world's children are vaccinated, and vaccines reach children in

remote areas, overcoming formidable obstacles of geography, conflict and poverty.

Even so, about 3 million people a year die of diseases that can be prevented with existing vaccines, such as measles, hepatitis B and tetanus. People die of vaccine-preventable diseases partly because approximately 25% of children, almost all of them in developing countries, do not receive a full set of immunizations (figure 1.2). And those who are immunized do not always get newer vaccines against some high-risk diseases because, though suitable vaccines exist, cost and other barriers have delayed their widespread introduction.

Low-income countries have benefited from R&D investments made in response to the market in high- and middle-income countries; but vaccines developed for high-income markets have been introduced in developing countries only after a considerable delay—typically 10–15 years or more (figure 1.3). For example, during the 1990s the use of a vaccine for Hib³ (a strain that causes some forms of pneumonia and meningitis) almost eliminated Hib-related diseases in high-income countries. But the vaccine remains too expensive for use in most low-income countries.⁴ As a result, an estimated 4.5 million unvaccinated children died from Hib-related diseases—mainly pneumonia—over the last decade (see figure 1.2).⁵ (Note that hepatitis B vaccination does

Box 1.1

The eradication of smallpox

An estimated 300 million people died from smallpox in the 20th century. As a result of a global effort, financed in part by foreign aid, the disease has been eradicated.

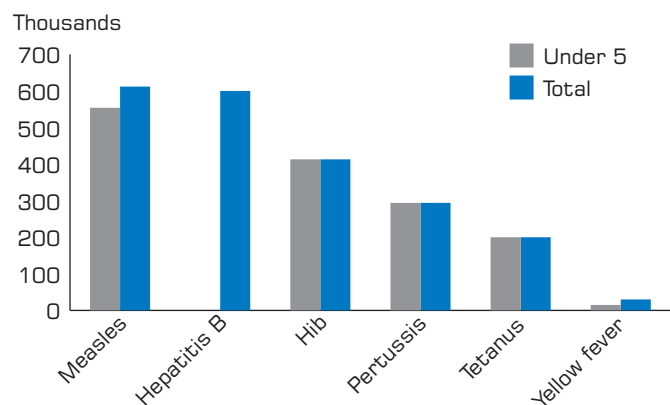
In the middle of the 20th century there were approximately 10–15 million cases of smallpox in more than 50 countries, and 1.5–2 million people died of the disease each year. Smallpox killed about a third of the people it infected.

In 1965 international efforts to eradicate smallpox were revitalized by a new Smallpox Eradication Unit at the World Health Organization and a pledge for more technical and financial support from the campaign's largest donor, the United States. Endemic countries were supplied with vaccines and kits for collecting and sending specimens, and vaccination was made easier by the provision of bifurcated needles. An intensified effort was led in the five remaining countries in 1973, with the surveillance and containment of outbreaks. By 1977 the last endemic case of smallpox was recorded in Somalia. In May 1980, after two years of surveillance and searching, the World Health Assembly declared that smallpox was the first disease in history to have been eradicated.

The cost of the smallpox campaign between 1967 and 1979 was \$23 million a year. International donors provided \$98 million, while \$200 million came from the affected countries.

Source: Levine and others (2004).

Figure 1.2
A million and a half children died from vaccine-preventable diseases in 2002



Source: WHO (2004c).

not prevent child deaths, but it prevents adult deaths if it is given to children early enough.)

More investment needed in vaccines for diseases concentrated in developing countries

Over and above the experience of delayed introduction of new products, desperately needed new vaccines simply may not be developed at all. Today, the health needs of children in the poorest countries are now quite different than those of children in Europe, Japan and the United States.

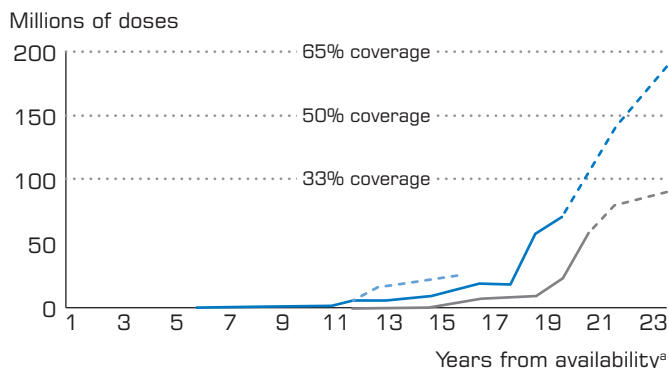
Fifteen years ago, a child born almost anywhere in the world received more or less the same basic vaccines—DTwP (diphtheria, tetanus and whole-cell pertussis [whooping cough]), OPV (oral polio vaccine) and BCG (tuberculosis).⁶ Over time, however, as

major childhood killers like measles were conquered in wealthy countries, new vaccines that are quite specific to rich-world conditions were developed. In some cases, vaccines were enhanced to decrease the (already very low) risks of adverse reactions. In general, these vaccines are costlier to produce. As a result of these changes, a child born in the rich world today receives different vaccines than a child in the developing world (figure 1.4).⁷

The priority diseases for poor countries are not the main priorities for rich countries. AIDS is a leading cause of death in the low-income countries, but it is not even one of the top 10 killers in high-income countries. Diarrhoeal diseases, malaria and other childhood diseases also appear on the developing world's top 10 causes of death, but are nowhere on the equivalent list for rich countries. Communicable diseases are the cause of 56% of the disease burden in low-income countries, and just 6% of the disease burden in high-income countries (table 1.1). The target product characteristics are also different: heat stability, safety and affordability continue to be major concerns for the developing world, while the developed world is driving toward very low risk vaccines even if this substantially adds to the cost.

As the pharmaceutical industry has responded to the health needs of the world's better-off, diseases that are concentrated in the poorest populations have largely been neglected (see table 1.1). The spectrum of available vaccines, even if used comprehensively, would not solve the major health problems facing the developing world.

Figure 1.3
Years from availability in developing countries for hepatitis B and Hib

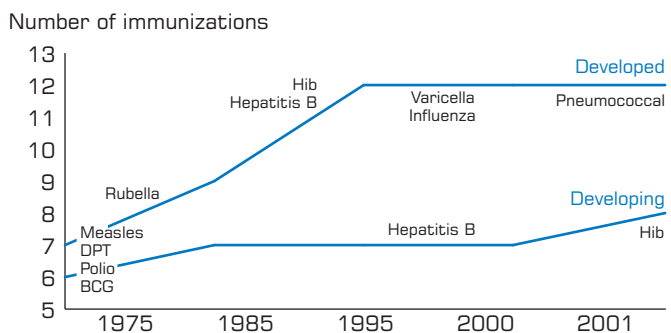


--- Hepatitis B, all developing countries
 --- Hepatitis B, all developing countries, excluding China, India and Indonesia^b
 --- Hib, all developing countries^c

a. Based on GAVI estimates for Vaccine Fund-eligible countries, plus countries that introduced the vaccine prior to GAVI. Last 5 years are estimates.
 b. Excludes China, India or Indonesia because of the high uncertainty whether they will introduce the vaccine or because they may use it only if manufactured locally.
 c. Coverage in all Vaccine Fund-eligible countries, including China, India and Indonesia (total of 95 million children).

Source: World Bank, Bill & Melinda Gates Foundation and GAVI (2002).

Figure 1.4
Vaccination gaps between children in rich and poor countries



Source: Batson (2001).

AIDS, tuberculosis and malaria account for about 5 million deaths a year; there is no effective vaccine for any of these three diseases, and the science for each is at an early stage. Pneumococcus is estimated to kill 1.1 million people a year, and rotavirus 0.8 million. For pneumococcus, vaccines are being developed, but they will need to be adapted to protect against the serotypes that account for the burden of disease in developing countries (box 1.3). Even once vaccines have been licensed for use, previous experience suggests that it will be many years before they are widely available at prices affordable to most developing countries. The form of the disease

they protect against may not be the form that is most common in developing countries. Other diseases primarily affecting the developing world for which no vaccines are available include shigella, schistosomiasis, leishmaniasis, chagas disease and dengue.⁸

This means that the developing world's previous source of affordable vaccines—residual supply from the developed world, at tiered prices—is no longer a reliable model. When new products are developed with the rich world—not the poor—in mind, diseases concentrated in the developing world are left behind. Not only would vaccines suitable for the developing world reduce the burden of disease, but it is generally believed that these health improvements would have substantial positive impacts on economic growth and poverty reduction (WHO 2003c) (box 1.2).

Table 1.1
Global burden of disease in 2002,
disaggregated by cause

Cause	Percent of total world disease burden	Percent of total disease burden in high-income countries	Percent of total disease burden in low-income countries
Communicable, maternal and perinatal diseases	41.0	6.2	56.4
Infectious and parasitic diseases	23.9	2.5	34.1
HIV/AIDS	5.8	0.6	7.6
Tuberculosis	2.4	0.1	3.0
Malaria	3.0	0.0	4.9
Respiratory infections	6.1	1.2	8.4
Other	11.1	2.5	13.9
Noncommunicable conditions	46.7	84.7	32.6
Malignant neoplasms (cancers)	5.1	14.7	2.4
Cardiovascular diseases	9.9	15.3	7.3
Other	31.7	54.7	22.8
Injuries	12.2	9.1	11.0

Note: Figures are disability-adjusted life years (see chapter 5 for definition). Country classifications are from World Development Indicators (World Bank 2003), based on World Bank estimates of 2001 gross national income per capita. Data for upper- and lower-middle-income countries are not shown.

Source: WHO (2003c).

Pharmaceutical development is a risky investment decision

R&D-based pharmaceutical companies and biotechnology firms are in a risky business. Their business model is to place smart

Box 1.2

Public health and economic growth

Public health matters because health measures offer the opportunity to save millions of lives and improve the quality of life for millions more. Many argue that improving health could also have a major impact on economic development, in part through a direct impact of increased life expectancy. Estimates are controversial, but one estimate by Jeffrey Sachs is that countries with intensive malaria grew 1.3% less per person a year; and that a 10% reduction in malaria was associated with 0.3% a year higher growth.^a A study of the United States found that more than half the growth of real income in the first half of the 20th century was attributable to declining mortality.^b In other words, reducing the burden of disease can make a direct contribution not only to achieving the health-related Millennium Development Goals, but more generally to the lives and prosperity of the developing world.

a. Gallup and Sachs (2000).

b. Nordhaus (2003).

bets on science in the face of imperfect market information. Firms get their competitive edge from doing this well. Vaccine development can take 7–20 years for basic research, clinical testing, regulatory approval, production and distribution—and at each of the stages, even the most promising candidates can fail to perform as hoped.

The investment costs are high. Estimates of the total cost vary, depending in part on what is measured. The range is from several hundred million dollars to more than \$1.5 billion. One often-cited study finds a cost of \$802 million for a new medicine, up to the point of regulatory approval.⁹

One reason that these estimated costs are so high is that these investments are uncertain: of all the candidate products that enter

development, only a small proportion will be successful, and far fewer will become “blockbusters” that earn a significant return for the company. For vaccine companies to stay in business, each successful product has to recover not only the costs of its own design and development, but also the costs of the unsuccessful candidates.

The development of new products is, in effect, the outcome of a series of bets placed on emerging scientific pathways, based on a hard-nosed analysis of the competitive landscape and some reasonable estimates of the eventual market size and willingness to pay. The companies that do this best undertake their own research and work in partnership with biotech companies, research scientists, academics and others. The final product combines the

Box 1.3 Pneumococcus

The bacterium *Streptococcus pneumoniae* is the most common cause of severe pneumonia worldwide. It also causes meningitis, septicaemia and ear infections.

Although estimates of its death toll are made difficult by various factors, the pneumococcus bacterium (*Streptococcus pneumoniae*) is thought to kill 1.1 million people worldwide each year, most of them young children and infants.

In developing countries as many as 1 in 10 deaths in young children is attributed to this infection. Although vaccines for adults and children ages two and older have been available for years, they have not been suitable for the babies and toddlers who are most vulnerable to the disease because the current vaccines do not stimulate an appropriate immune response.

However, a new conjugate vaccine that is highly effective in infants has recently been approved for marketing by the Food and Drug Administration (FDA) in the United States, and several more vaccines are in late stages of development. But it is unclear whether these will be as effective in developing country settings as they are in developed countries.

Pneumococcal vaccines protect by stimulating antibodies against the specific polysaccharide (complex sugar) capsules that cover the bacteria. There are more than 80 specific pneumococcal capsular polysaccharides. The pneumococcal conjugate vaccine licensed by the FDA stimulates the production of protective antibodies against the seven serotypes that most frequently cause invasive disease in the United States. However, this “7-valent” vaccine does not stimulate antibodies against two serotypes, 1 and 5, which together are thought to be responsible for 12%–25% of invasive pneumococcal disease in many developing countries.

With such countries in mind, researchers and the vaccine industry have developed 9-valent and 11-valent pneumococcal conjugate vaccines that stimulate antibodies against serotypes 1 and 5. These vaccines are the subject of large-scale field trials in several countries in Africa, Asia and Latin America. Recommendations about the use of the new pneumococcal vaccines among infants in developing countries will depend on the results of these trials, the initial results of which have been spectacularly positive.

scientific knowledge, innovation and intellectual property of a large number of partners.

Despite these uncertainties, the market for medicines in the developed world succeeds in generating important new products. Effective and innovative drugs and vaccines are invented, tested, licensed and produced. The functioning of the market for affluent countries depends on patents and regulatory protection, which grant the manufacturer a temporary period of market exclusivity. This means that manufacturers are able to charge consumers a price high enough not only to cover the cost of production but also the costs of research and development. Market considerations play an important part in each stage of the process as possible medicines move from investment in basic research, through to clinical trials, licensing, production and supply (figure 1.5).

By offering the opportunity to charge temporarily higher prices for the medicines, market exclusivity acts as a “pull” mechanism,

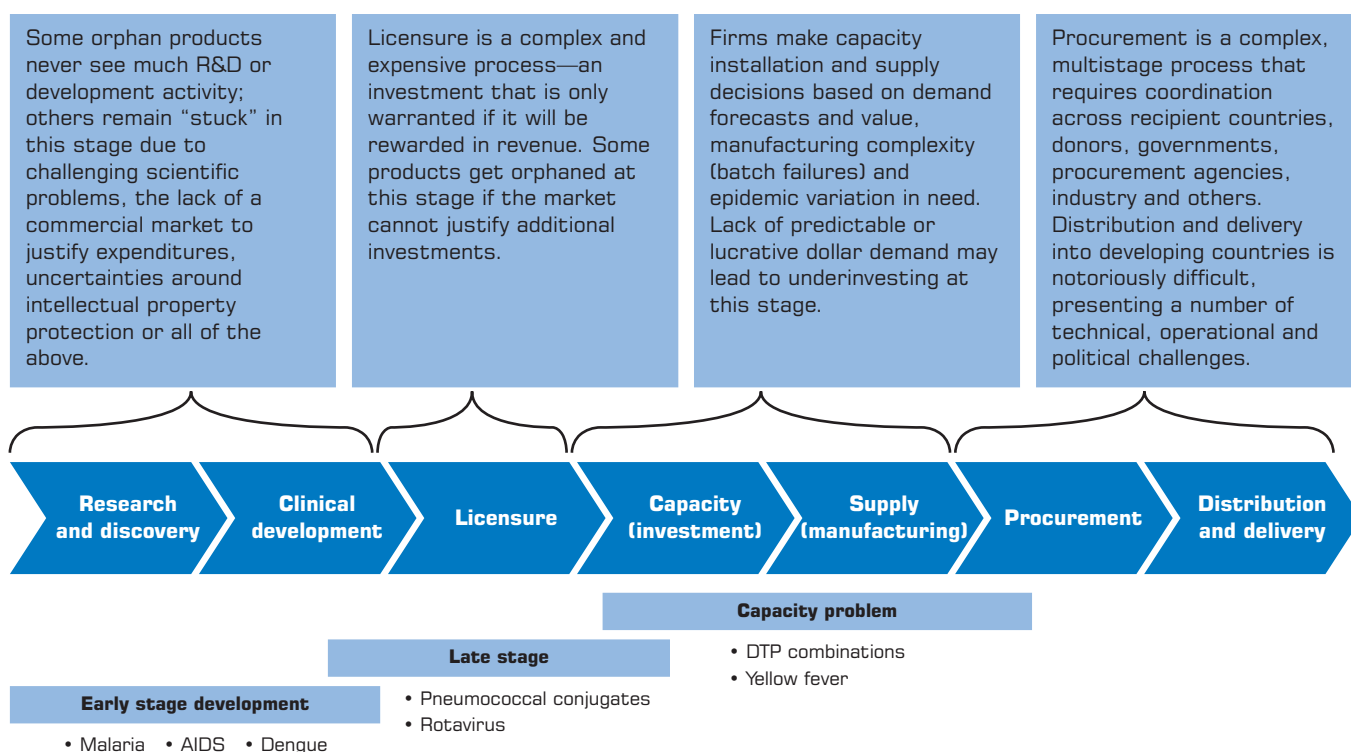
providing pharmaceutical companies with sufficient incentive to make risky investments, some of which will eventually result in life-saving medicines of enormous social value.

The small market for vaccines for developing countries

The total market for vaccines for developing countries is about \$500 million a year¹⁰ (figure 1.6), though it is growing as a result of increased spending through GAVI, which has spent some \$530 million since it was launched in 2000.¹¹

Total spending on health in the least developed countries averages \$17 a person a year, of which about \$6 a person is from the country’s government budget. For slightly better-off low-income countries, the average is about \$36 a person a year.¹² (The equivalent figure for high-income countries is \$2,263 a year.)

Figure 1.5
Vaccine development pipeline



The differentials in health spending are reflected in the vaccine market. The global market for vaccines is about \$6 billion a year—accounting for only 1.5% of global pharmaceutical sales.¹³ Global sales of all vaccines combined are roughly equivalent to annual sales of a single blockbuster drug such as Lipitor or Prilosec.¹⁴ Developing-country markets account for about half the total vaccine sales by volume, but provide only about 5%—or less—of total revenues from vaccine sales. So developing-country vaccines currently make up a negligible proportion—less than 0.1%—of the value of pharmaceutical sales.

Public procurement policies must balance long- and short-term interests

From a commercial perspective, the arrangements that developing countries and development agencies use to buy medicines may compound the problem of an anemic market size. Most vaccines are bought by public health authorities or on their behalf by the procurement divisions at agencies such as the United Nations Children’s Fund (UNICEF). Once firms have sunk R&D resources on a vaccine, governments—in the interests of protecting scarce health budgets—have an incentive to use their role as dominant purchasers, regulators and arbiters of intellectual property rights to negotiate the lowest possible price. Given the very limited funds available for health, even with international donor support for immunization programs, achieving a low price

is an essential way for these authorities to buy valuable health products for as many people as possible.

But the short-term need to get vaccines to many people competes with the long-term need to ensure that firms can meet the costs of R&D and also provide returns to shareholders. This is particularly problematic when both developing-country governments and donor agencies have become accustomed to buying vaccines at “pennies per dose.” Buying vaccines at very low prices means that firms receive little more than the cost of production, not enough to recover the costs of the original R&D. Knowing in advance that buyers will want to push prices down in this way, it is difficult for firms to plan to invest in these products at all.

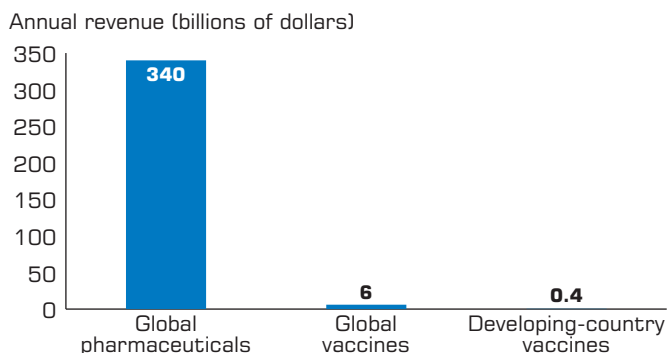
Uncertainties in demand, in addition to the monopsony, increase the risks. International agencies’ procurement arrangements typically do not bind the purchaser to buy the full number of doses for which tenders are issued. The quantity purchased may be much less than expected because of unforeseen calamities, volatility in the availability of donor or domestic funding, weak information systems and many other shortcomings in the ability to forecast demand. Given nonbinding contractual arrangements, the quantity risk lies entirely with the supplier.

The need to reduce the lag time

Pooled procurement and uncertain demand are not the only factors that create an unfavorable risk-reward profile. Increasingly, activists and public-policy makers are unwilling to accept long lag times between the availability of life-saving drugs in the rich countries and access to those products at prices affordable to developing countries. The pressure on donors and firms to make antiretroviral drugs available to those with HIV/AIDS has brought this issue into sharp relief, but it is also the topic of active debate in the immunization field.

Pharmaceutical firms know when they are planning future research that, once a medicine is available, governments will wish to negotiate the price down and the company will come under pressure from public opinion to make important medicines available as cheaply as possible. In extreme cases, the developer of an essential new medicine may face compulsory licensing. If the firm does not expect to be able to recover its development costs at the price it will be able to charge, it will hesitate to invest in developing the medicine in the first place.¹⁵ As one senior industry executive

Figure 1.6
Markets for vaccines are much smaller than those for pharmaceuticals



Source: Batson (2001).

said, “Our worst nightmare would be to discover a vaccine for AIDS. We would be forced to give it away.”

With no valuable market, the prospects for the development of new vaccines to prevent or mitigate the severity of disease concentrated in low-income countries through innovation in the private sector are not promising. As we shall see in chapter 2, only 13 (1%) of the new chemical entities brought to market from 1975 to 1997 were specifically for diseases of developing countries; and of these, only 4 were the direct results of R&D activities of the pharmaceutical industry targeted at new human products.¹⁶ While there is some modest commercial investment, we are some way away from providing incentives that would engage the full resources and energy of the pharmaceutical and biotech firms in finding these solutions, which are essential to improving human health.