CHAPTER 4

HEPATITIS B VACCINE:
Access to Vaccines
**Hepatitis B** is a serious liver infection caused by the hepatitis B virus (HBV). HBV is transmitted through blood and infected bodily fluids. The virus can spread through direct blood-to-blood contact, unprotected sex, unsafe injections and blood transfusions, and from a woman infected with HBV to her newborn during the delivery process. Because of similar transmission paths, there is a high degree of HBV and HIV co-infection. An estimated 10% of people living with HIV worldwide also have HBV infection.

When people first contract HBV, they experience a period of acute infection, in which they may either have no symptoms or become seriously ill. While many people recover completely from the acute infection, those who still have the virus in their blood for more than six months are diagnosed with chronic infection. Most of the disease burden associated with HBV is from the chronic condition. Though many chronic sufferers do not feel sick for decades after infection, in later life they can die from cirrhosis (a serious liver condition characterized by irreversible scarring of the liver) and liver cancer (a malignant tumor of the liver, also called hepatocellular carcinoma). Approximately 1.8 billion people (one third of the world’s population) have serological evidence of HBV infection. Of these, WHO estimates that 360 million people have chronic infection, and at least 600,000 chronically infected people die annually from liver cancer and cirrhosis.¹ Those people who have hepatitis B but do not have symptoms (because their immune systems do not see the virus as foreign) are known as carriers and can unintentionally infect other people.

Age is a key factor in determining the outcome of HBV infection. Ninety percent of adults with acute infection recover and rid the virus from their blood, so that only 5–10% go on to develop chronic infection. However, of infants who become infected with HBV in the first year of life, 80–90% will develop the chronic condition, and 30–50% of children aged one to four years will do so.² Preventing HBV infection among children ages five years and younger is therefore a priority in tackling hepatitis B, and this is now possible through vaccination. Estimates suggest that at least 85–90% of deaths associated with hepatitis B can be prevented using this technology.³

The HBV vaccine first became available in 1981, but introduction in developing countries in the 1980s and 1990s was slow and limited. This case study examines the barriers to access for the hepatitis B vaccine during this time period and how key groups in the architecture of hepatitis B vaccine—including both WHO and a product champion known as the International Task Force on Hepatitis B Immunization—effectively undertook a series of actions to solve major problems
of availability, affordability, and adoption in collaboration with a range of partners, including international agencies, private foundations, non-profit organizations, vaccine producers, and developing country governments. The combined efforts led to a change in the global architecture for hepatitis B vaccine access, resulting in dramatic increases in the vaccine’s use in the 2000s.

**Product Development (Phase 1)**

While studying hepatitis during and after World War II, the British doctor F. O. MacCallum identified two types of the disease and named them hepatitis A and hepatitis B (see Table 4.1 for a description of the different types of viral hepatitis). In the 1950s and 1960s, researchers attempted to find the causal agent for these two categories of hepatitis. An important breakthrough came in the 1960s, when Baruch Blumberg discovered a blood test for the surface component of the hepatitis B virus. This discovery occurred at a time when Blumberg was investigating a different topic—whether people have inherited differences (rather than just environmental differences) in susceptibility to disease. In the course of collecting and analyzing blood samples from populations around the world, Blumberg and a team of researchers based at the U.S. National Institutes of Health developed a method for testing the blood of people who had received multiple blood transfusions. This method allowed them to test the hypothesis that patients with multiple blood transfusions would develop antibodies against foreign proteins that they had not inherited. Blumberg and his team used this blood test in their search for genetic differences linked to disease susceptibility. In doing so, they found an antibody that had never been seen before which reacted with a protein found in an Australian aborigine’s blood sample. They called this protein the *Australian antigen*. (For definitions of antibodies, proteins, and antigens, see the Glossary.)

For a time, the researchers were unsure of the significance of the Australian antigen. In 1966, virologist Alfred Prince of the New York Blood Center suspected that the antigen was associated with the hepatitis B virus and began investigations that suggested the Australian antigen was linked to the development of hepatitis B. In the years that followed, other researchers independently confirmed that the Australian antigen was part of the virus that caused hepatitis B, and the antigen’s name was changed to HBsAg, standing for hepatitis B surface antigen. Blumberg won a Nobel Prize in Medicine in 1976 for his part in this discovery. According to historian William Muraskin, this finding had a “revolutionary impact on medical science” because it allowed researchers to proceed with the
In the late 1960s, Blumberg developed a prototype hepatitis B vaccine with his colleague, Irving Millman, at the Fox Chase Cancer Center (FCCC) in Philadelphia. This discovery forged a new approach to vaccine development. The three previous methods of vaccine development involved (1) using whole viruses or bacteria that had been killed to prevent infection, (2) using weakened strains of pathogenic organisms that produced mild or no symptoms when injected as a vaccine but protected recipients from the more serious wild strains, and (3) using whole viruses that did not cause disease themselves but were closely related to viruses that did. Blumberg and Millman’s new method used only subunits of human virus (the HBsAg particles) obtained from the blood of hepatitis B carriers. As Blumberg recalls in his personal account of the vaccine’s development,

“We took antigen from individuals who had a great deal of it and used it to inoculate others who didn’t have any: a “people’s vaccine,” as we sometimes jokingly called it. Our ability to do this was based on the fact that the virus produced very large quantities of the small, noninfectious particles containing only the surface antigen.”

The FCCC patented the method for this prototype hepatitis B vaccine in 1969 but was not equipped to test and produce the vaccine. Blumberg and his
colleagues thus sought a pharmaceutical manufacturer to carry out these tasks.¹⁰ New Jersey–based Merck & Co. was interested in the vaccine if the company could have exclusive patent rights.¹¹ But the funder of Blumberg’s research, the National Institutes of Health, insisted that the technology be licensed to more than one company to avoid a monopoly situation. After extensive discussions between Blumberg, his colleagues, and executives at Merck, a solution was found that gave the company exclusive rights to the vaccine in markets outside the United States. The company reached agreement on a license for the technology from the FCCC in 1975.¹² Merck then developed a more sophisticated hepatitis B vaccine based on Blumberg and Millman’s original concept. In 1981, Merck’s Heptavax became the first hepatitis B vaccine on the market. At introduction, one dose cost $30. In 1982, the Institut Pasteur of France introduced another hepatitis B vaccine known as HevacB. These vaccines are known as plasma vaccines because they both are derived from human blood.

At about the same time in the 1970s, Prince was also pursuing research on a plasma vaccine for hepatitis B. Prince wanted to develop a vaccine that was affordable to developing countries. He worried that Merck and Institut Pasteur used large and expensive centrifuges in the vaccine development process that would make the technology unaffordable for poor nations. In his work, he sought to develop a simple and inexpensive vaccine whose technology could be transferred to the countries that most needed the product.¹³ Prince ultimately decided on a flash heat purification method for his vaccine. This much simpler and cheaper procedure increased the potency of the vaccine and reduced the size of doses.¹⁴ In addition, the vaccine required a smaller amount of the most expensive ingredient, the blood of hepatitis B carriers. Prince worked with a company in Korea, the Cheil Sugar Company, to develop this vaccine for commercial use at an affordable price for countries in Africa and Asia. In 1982, Cheil started producing this vaccine.¹⁵

Since 1981, the production of plasma hepatitis B vaccines has spread to companies in the United States, France, Republic of Korea, China, Vietnam, Myanmar, India, Indonesia, Iran, and Mongolia. But several barriers arose to producing large quantities of the vaccines. The most significant was the need for blood of hepatitis B carriers.¹⁶ Furthermore, some policy makers and end-users worried about the safety of the vaccine because it was derived from human blood.

A technological innovation helped resolve some of the problems with the plasma vaccine. In 1977, William Rutter and his team at the University of California began working on the development of a second generation of hepatitis B vaccines using DNA-recombinant technology. Their new vaccine was synthetically
prepared and did not contain any blood products. To make the vaccine, the researchers copied the genetic sequence of a protein contained in the hepatitis virus into a yeast cell, which was then cultured, purified, and prepared into a vaccine. Chiron Corporation, founded by Rutter and colleagues, began working with Merck to commercialize a hepatitis B vaccine using recombinant technology. SmithKline Beecham also began to develop a recombinant hepatitis B vaccine product. The U.S. FDA approved Merck's recombinant vaccine in 1986 (Recombivax HB) and, three years later, approved SmithKline Beecham’s product (Engerix-B). To achieve product development, Merck and SmithKline Beecham licensed three important patents belonging to Institut Pasteur, Biogen, and the University of California. They also needed licenses for more than 90 other patents for manufacturing processes such as isolation and purification.

The recombinant vaccines represented a major advance. They induce an immune response but cannot infect recipients with the hepatitis B virus. Other advantages of this new technology are its shorter production cycle (12 instead of 65 weeks), batch-to-batch consistency, and continuous supply of the material. On the other hand, because the recombinant technology was patent-protected, there was a limited number of producers for the resulting vaccines. Product prices at introduction were as high as $40 per dose, above the prices for the plasma vaccines. Despite the high prices, the recombinant vaccines soon pushed the plasma vaccines off the markets in North America and Western Europe. (Merck's Hepavax, for example, was discontinued in 1990.) The plasma vaccines, however, have continued to be produced and used elsewhere, as discussed below.

Today, recombinant hepatitis B vaccines are produced in Belgium, China, Cuba, France, India, Israel, Japan, the Republic of Korea, Switzerland, the United States, and Vietnam (see Table 4.2 for a list of recombinant products that have WHO prequalification). Hepatitis B vaccine is available from these manufacturers in monovalent forms (providing protection against hepatitis B only) and also in multivalent formulations combined with *Haemophilus influenzae* type b (Hib) vaccines, diphtheria-tetanus-pertussis (DTP) vaccines, inactivated polio (IPV) vaccines, and hepatitis A vaccines. Multivalent vaccines are beneficial because they can simplify delivery and can also cost less than two separate vaccines by eliminating expenses for separate vials, packaging, needles, syringes, and cold-chain storage expansion. In a following section, we discuss the factors that enabled the entry of new manufacturers to the hepatitis B vaccine market.

The product development phase for hepatitis B vaccine ended with the existence of plasma and recombinant vaccines, effective in preventing infections if
given either before or shortly after exposure to HBV. These innovations promised major benefits around the world. The challenge was to introduce the hepatitis B vaccine effectively into developing countries.

### Introducing Hepatitis B Vaccine in Developing Countries (Phase 2)

Approval of the plasma vaccines in the early 1980s produced only limited uptake in developing countries. The primary reason was the high price that made the vaccine unaffordable to governments. When Merck’s plasma vaccine first came on the market in the United States, it cost more than $30 per dose or nearly $100 for

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**Table 4.2 | United Nations prequalified hepatitis B vaccines, as of March 2008**

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<tr>
<th>PRODUCER</th>
<th>MONOVALENT AND COMBINATION HEPATITIS B VACCINE PRODUCTS</th>
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| Berna Biotech Korea Corp | • Hepatitis B<sup>a</sup> (recombinant)  
• DTP-HepB-Hib<sup>b</sup> |
| Bio Farma, Indonesia | • Hepatitis B<sup>a</sup> filled in Uniject  
• DTP-HepB<sup>b</sup> |
| Center for Genetic Engineering and Biotechnology, Cuba | • Hepatitis B<sup>a</sup> (recombinant) |
| GlaxoSmithKline, Belgium | • Hepatitis B<sup>a</sup> (recombinant)  
• DTP-HepB<sup>b</sup> (2 products)  
• DTP-HepB to be combined with Hib<sup>c</sup>  
• DTP-HepB + Hib |
| LG Life Sciences Ltd., Korea | • Hepatitis B<sup>a</sup> (recombinant) |
| Merck & Co., Inc., USA | • Hepatitis B<sup>a</sup> (recombinant) |
| Panacea Biotec, India | • Hepatitis B<sup>a</sup> (Enivac B)  
• DTP (Bio Farma)-HepB (PHB)<sup>b</sup>  
(1 dose) (1 dose) (Ecovac) |
| Serum Institute of India | • Hepatitis B<sup>a</sup> (recombinant)  
• DTP-Hep B<sup>b</sup> |
| Shantha Biotechnics Private Ltd., India | • Hepatitis B<sup>a</sup> (recombinant)  
• DTP-HepB<sup>b</sup> |


<sup>a</sup> Monovalent vaccine  
<sup>b</sup> A combination tetravalent vaccine including diphtheria-tetanus-pertussis (DTP) vaccines and hepatitis B (HepB) vaccine  
<sup>c</sup> A combination pentavalent vaccine including diphtheria, diphtheria-tetanus-pertussis (DTP) vaccines and hepatitis B (HepB) vaccine plus *Haemophilus influenzae* type b (Hib) vaccine
the necessary three doses. At this time, the traditional vaccines procured for the WHO Expanded Programme on Immunization (EPI) programs (polio, DTP, measles, and Bacillus Calmette-Guérin) cost less than $1 per child. The high cost of the first hepatitis B vaccines thus blocked their integration into the ongoing EPI programs.

A second reason for limited uptake of the plasma vaccine was related to policy makers’ and end-users’ concerns about safety because these vaccines came from human blood. These safety concerns led experts in some countries to question the wisdom of launching mass hepatitis B vaccination programs. Questions were raised about connections between hepatitis B vaccine and multiple sclerosis, leading to worried providers and parents in some countries. Although WHO and others examined these safety issues and declared them to be unfounded, the perception of health risks associated with plasma vaccines persisted among some national decision-makers and negatively influenced national adoption.

A third barrier affecting national adoption was a limited understanding of the extent of hepatitis B burden in many countries. Muraskin notes that while many countries in Asia were aware of their hepatitis B problems, African nations often lacked good understanding of or adequate concern about this health problem: “For most Africans, the continent suffered from so many pressing health problems that hepatitis B simply seemed to lack urgency.”

The fourth barrier was an availability constraint and involved delivery challenges for the vaccine. Children must receive three doses of hepatitis B vaccine to develop protective antibodies. WHO developed three integration options for countries to incorporate the vaccine into routine childhood immunization schedules (see Table 4.3). Two options involve a dose given as soon as possible after birth (within 24 hours). This dose is important in countries where a high proportion of chronic infections are acquired perinatally. But the difficulty of administering a birth dose, particularly in rural areas where mothers usually give birth at home, posed a major delivery challenge. Furthermore, in some countries, the immunization program was weak and under pressure to deliver the traditional EPI vaccines. Adding another vaccine to the program would stress an already overloaded health system and would require new logistics, training, and management.

These affordability, adoption, and availability problems contributed to limited national and global adoption of the new plasma vaccines. To address these barriers to access, three individuals working on hepatitis B in the developing world—Prince along with Richard Mahoney (director of Program for Appropriate Technology in Health or PATH) and James Maynard (director of Hepatitis
Branch, Centers for Disease Control)—established a new entity in April 1986: the International Task Force on Hepatitis B Immunization. The Task Force received initial funding from the Rockefeller Foundation ($50,000) and the James S. McDonnell Foundation (almost $2.5 million for three years) to accomplish two main goals: (1) to identify practical ways for integrating hepatitis B vaccination into mass infant immunization programs, and (2) to ensure the production of hepatitis B vaccines in adequate quantities and at low prices so that developing countries could conduct mass infant immunization. The Task Force sought to achieve these objectives through a series of demonstration projects in Asia and Africa (Indonesia, Thailand, China, Kenya, and Cameroon). The first two demonstration projects were in Indonesia and Thailand, with Mahoney directing the Task Force and PATH serving as the in-country implementing partner.

The Task Force first sought to lower the cost of the plasma vaccine. Prince was already working with the Korean firm, Cheil Sugar Company, to develop his
prototype vaccine. The Task Force negotiated an agreement with Cheil to establish a $1 per dose price for a minimum of 5 million doses. Achieving this commitment from Cheil was a major breakthrough for the Task Force in pushing product prices down. It did not, however, provide them with an affordable price for their first pilot project in Indonesia, since that project required less than 5 million doses. The Indonesian government, therefore, decided to foster competitive pricing through a sealed international bid and tender, as recommended by the Task Force. Many companies participated in the bid, with the lowest one ($0.95 per dose) coming from another Korean company, Korea Green Cross Corporation, for its plasma vaccine.

With this price, the Task Force, along with PATH and the Indonesian government, could proceed with its first demonstration project in Indonesia. But government officials initially resisted moving forward with the project for many reasons:

*The basic Expanded Programme for Immunization (EPI) vaccines were not being given to most children; there was not enough money to educate the public on health matters; there were not enough syringes for current vaccinations—they were either being used over and over again or illegally diverted to the private market; the cold chain required for vaccines was inadequate and the limited resources that existed were needed for polio and measles; high infant mortality due to diarrheal diseases, tetanus, or upper respiratory tract infections was more important; malaria was spreading.*

Finally, and with the backing of Indonesian President Suharto who had lost a close colleague to liver cancer, the Task Force and PATH convinced government officials to implement the pilot project. An important component of this project was the fine-tuning of delivery methods for the birth dose, part of which was the piloting of hepatitis B vaccine prefilled syringes (heat stable for one month outside the cold chain). The demonstration project was successful and, as a result, the Indonesian government decided to begin universal hepatitis B immunization in 1991. Meanwhile, the Task Force continued model programs elsewhere and helped several countries develop international tenders. The price of the plasma vaccine continued to drop, reaching $0.65 per dose offered to the Philippines in 1991.

Official policy development on hepatitis B vaccine at the global level began in the early 1990s. In 1991, WHO and the Task Force convened an international meeting in Cameroon on hepatitis B. The meeting concluded that hepatitis B ranked among the world’s most pressing health problems, that vaccination could be feasibly integrated into EPI without harming the program, and that a global
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fund should be established to purchase and deliver the vaccine.\textsuperscript{32} Later that year, the Global Advisory Group of the EPI endorsed these views and set the following timetable: Hepatitis B vaccine should be integrated into national immunization programs in countries with hepatitis B carrier prevalence of 8% or greater by 1995 and in all countries by 1997. The World Health Assembly endorsed this recommendation in 1992, and two years later it called for an 80% decrease by 2001 in the incidence of new hepatitis B virus carriers in children.\textsuperscript{33} The Global Advisory Group also recommended that the new Children’s Vaccine Initiative work to create a global vaccine fund for hepatitis B vaccine and other vaccines.\textsuperscript{34}

The Task Force, by pushing adoption of the hepatitis B vaccine at both national and global levels, achieved several important tasks that promoted greater access. First, the Task Force pushed the product price of the plasma vaccine to $1 per dose through the Indonesian bid and tender agreement. Second, the group helped create consensus on hepatitis B vaccine integration into the EPI through the Cameroon meeting with WHO. Furthermore, the Task Force and PATH showed practical ways of delivering the vaccine in developing countries (particularly the birth dose) through the demonstration projects. The demonstration projects also helped counteract the negative perceptions of safety in the countries in which they were implemented and at the global level as well.

Despite these important achievements and despite a growing global focus on the hepatitis B vaccine, by 1997 it became clear that WHO’s targets would not be met. In 1991, when the EPI made its recommendation, approximately 20 countries (mostly in North America, Europe, and Asia) were routinely using the vaccine.\textsuperscript{35} By 1995, only 35 of 90 countries with prevalence rates greater than or equal to 8% had begun hepatitis B vaccination programs.\textsuperscript{36}

By the end of the 1990s, the central challenge for hepatitis B vaccine advocates was the lack of affordability for governments in developing countries. The Task Force demonstrated this problem in Kenya. EPI staff wanted to integrate the vaccine into their program but could not afford the price of $1 per dose.\textsuperscript{37} Though product prices had decreased significantly, they were still not low enough for many developing country governments. Vaccine advocates needed to find other ways to create further price decreases.

### Scaling Up Hepatitis B Vaccine (Phase 3)

In the early years of the 2000s, access to hepatitis B vaccine increased significantly in the developing world. The entry of new manufacturers into the market in the mid-1990s created more competition and drove down prices. Also the creation of
the Global Alliance for Vaccines and Immunizations (now known as the GAVI Alliance) in 1999 spurred a growth in access, especially as the new organization gave priority to underutilized vaccines such as hepatitis B vaccine.

These two developments occurred in the context of a changing international vaccine market. Since the 1970s, global vaccine production shifted from the public to the private sector. Production objectives, therefore, became increasingly based on market considerations rather than public health needs. This trend accelerated in the 1990s, with pharmaceutical company mergers leading to less flexibility in vaccine production. In the late 1990s, developing countries experienced vaccine shortages when industrialized countries began to introduce more expensive vaccines based on new technology (such as recombinant vaccines), and the production of older vaccines declined. Previously the same vaccines had been used in both rich and poor countries. But now vaccine producers began phasing out production of the older, less expensive vaccines that were being used mainly in developing countries. Between 1998 and 2001, 10 out of 14 producers partially or completely stopped manufacturing traditional vaccines. By 2002, the UNICEF Supply Division (UNICEF’s global procurement operation) was buying 65% of its traditional vaccines (apart from oral polio vaccine) from only two manufacturers.38

These structural changes in the global vaccine market had important consequences for both availability and affordability. The traditional vaccines became less available while their prices increased. UNICEF responded by developing a “vaccine security strategy” that involved: (1) giving manufacturers sufficient guarantees through purchasing agreements, (2) looking for funding to cover vaccine requirements, and (3) engaging in long-term forecasting to allow companies sufficient time to increase production if necessary.39 With this new strategy, UNICEF’s role shifted from vaccine buyer to strategic partner with producers. This changing context of global vaccine production had critical implications for hepatitis B vaccine access.

Entry of New Manufacturers into the Market
Merck played a major role in the global market for hepatitis B vaccine. The company launched the first plasma hepatitis B vaccine in 1981. Five years later, Merck introduced the first recombinant hepatitis B vaccine. But a host of new companies soon joined the field.

In the late 1980s, new manufacturers from a range of countries (including China, Japan, and Korea) entered the market with their own hepatitis B vaccine products. At the same time, the International Task Force for Hepatitis B
Immunization was negotiating lower prices for plasma vaccine from two Korean manufacturers (Cheil and Green Cross, as noted above). In the following decade, several Indian manufacturers entered the hepatitis B vaccine market. Increasingly, these developing country firms were making the recombinant rather than the plasma vaccine. At the same time, established vaccine producers shifted from traditional vaccine production to newer technologies and more costly vaccines.

The entry of these new producers created more price competition. Prices for the recombinant vaccine reached as low as $0.54 per dose in 1999. With the new competition, companies sought new markets for their products. Some applied for WHO prequalification so they could sell their vaccines to developing countries through UNICEF’s Supply Division.

The higher profits of the new recombinant technology provided a major incentive for producers to enter the hepatitis B market. The expiry of patents also encouraged the entry of new firms; for example, Biogen's patent on recombinant technology for hepatitis B vaccine expired in many countries by the mid-1990s. Additional factors explain the entry of new manufacturers as well. Mahoney provides a useful analysis of these factors in regard to Korean companies. Having worked with the Task Force to supply plasma vaccine, Korean producers saw that an international market for the vaccine existed. Three vaccine producers (Cheil, Green Cross, and LG Chem) then began developing the recombinant vaccine. Green Cross achieved this by acquiring patented technology from Rhein Biotech of Germany. This involved the biotechnology company taking a controlling interest in Green Cross. LG Chem learned how to make the vaccine through a joint venture with the Chiron Corporation. Cheil tried to develop its own technology but was ultimately unsuccessful.

Mahoney lists several facilitating factors that led to the entry of the Korean manufacturers into the international market and subsequent WHO prequalification of their products. The Korean Food and Drug Administration had recently improved its operations. Staff from WHO had required these improvements as a condition for prequalifying Korean producers, and the Korean government complied. The establishment and operation of clinical testing sites (with national public and private support) allowed Korean producers to provide high-quality data to national regulatory authorities in developing countries. This is important because regulatory agencies in developing countries have increased their requests for high-quality information from producers instead of simply registering a vaccine because it is licensed in the country of manufacture.
The entrance of Indian firms into the hepatitis B vaccine market in the 1990s also helped promote price competition. New players entered the domestic market in India because of profit margins, high demand, and the possibility of bulk purchases through India’s national immunization program. Some of these companies expanded globally and sought WHO prequalification.

In sum, starting in the late 1980s and through the next decade, a number of new manufacturers entered the hepatitis B vaccine market from several developing countries, propelled by market factors and assisted by actions of the Task Force and WHO. The resulting competition helped push down prices dramatically. By 2006, the UNICEF Supply Division price for recombinant, monovalent hepatitis B vaccine reached $0.25 per dose. Further support for the international market for this vaccine came through the actions of a new entity—the GAVI Alliance.

**The GAVI Alliance**

Restructuring the global architecture to promote hepatitis B vaccine provided a major impetus for increased adoption, both global and national. As mentioned previously, the Global Advisory Group of the EPI argued in 1991 for the creation of a global vaccine fund to finance childhood vaccines, including the hepatitis B vaccine, in developing countries. The group recommended that the Children’s Vaccine Initiative (CVI) take on this task. The CVI was established in 1990 by five agencies—UNICEF, WHO, the United Nations Development Program, the World Bank, and the Rockefeller Foundation—with the goal of developing new and improved vaccines and was placed within WHO. One main objective was to bring the public and private sectors closer together to achieve cooperation on vaccine development. Toward the end of the 1990s, it became clear that these efforts to develop new vaccines were failing. The CVI then turned its focus to the introduction of existing underutilized vaccines in developing countries, such as those for hepatitis B, yellow fever, and *Haemophilus influenzae* type b (Hib).

CVI’s new goal, however, also proved elusive. Private industry supported CVI’s new focus because it felt that public-private cooperation on the development of new vaccines was premature until problems of access to current vaccines were tackled. The public sector’s argument that industry had neglected to develop new vaccines for diseases of the poor was not persuasive when existing vaccines, such as hepatitis B, were little used in developing countries. The CVI, however, lacked the financial and political power to make the private sector a full partner in these activities. Experts in both the public and private sectors argued that no single organization (i.e., WHO) could carry out this work to expand access to existing
vaccines and that a committed partnership of international agencies was needed. In 1999, WHO, UNICEF, the World Bank, the Bill & Melinda Gates Foundation’s Children’s Vaccine Program, the Rockefeller Foundation, the International Federation of Pharmaceutical Manufacturers & Associations, and some national governments established the GAVI Alliance. Importantly, the private sector was given an equal place next to the UN agencies in the new initiative. Specifically, private industry received two seats on the 16-member board of directors, one each for developed and developing country representatives.

The GAVI Alliance saw itself less as an organization and more as a “movement aimed at ensuring that the universal childhood immunization agenda set up in the 1980s is reenergized, expanded, and brought up-to-date.” Tore Godal, a Norwegian immunologist and leader in global health, became executive secretary of the new initiative, and the board of directors took responsibility for GAVI’s governance. The founding agencies were concerned that immunization rates had leveled off in some countries and declined in others. Their goal in establishing the GAVI Alliance was to fulfill the right of every child to be protected against vaccine-preventable diseases of public health concern. The GAVI Alliance and the GAVI Fund (previously called the Vaccine Fund) began with an initial Bill & Melinda Gates Foundation grant of $750 million over five years. For these years, the Gates funding comprised half of GAVI’s resources, with grants also provided by the United States, Norway, the Netherlands, and the United Kingdom. In early 2005, the Gates Foundation provided a second grant of $750 million for another 10 years. The goal is to reduce Gates funding to less than 20% of GAVI’s total resources within that time.

The GAVI Alliance uses a business model based on two principles. First, the GAVI Fund is used to finance the procurement of new and underused vaccines for developing countries. The GAVI Alliance prioritizes vaccines for hepatitis B, as well as for *Haemophilus influenzae* type b, pneumococcal, rotavirus, yellow fever, and measles (second dose). Along with procurement of these vaccines, the GAVI Fund emphasizes the use of combination vaccines and vaccine vial monitors (see chapter 7) to reduce wastage, as well as “auto-disable” injection equipment to prevent unsafe injections.

Second, the GAVI Alliance provides performance-based financial incentives for improving immunization infrastructure and capacity to governments of countries with low immunization rates. GAVI soon discovered that its focus on strengthening “immunization systems” was too narrowly conceived and that broader health-system failures often constrained a country’s ability to immunize...
more children.\textsuperscript{53} At the same time, many global health experts argued that initiatives such as GAVI should address sectorwide issues, rather than focusing only on single health issues. In response, GAVI adapted its model to provide support for broader health-system improvements (for example, raising the frequency of supervisory visits).\textsuperscript{54}

GAVI also targets its support to the poorest countries in the world. As of March 2008, 72 countries were eligible (countries with an annual Gross National Income per capita below $1,000). The GAVI Alliance offers five kinds of support. The first type of support is for immunization services. Countries can apply for an annual grant of $20 per additional child targeted for immunization in the “investment phase” (the first two years of the country’s multiyear plan). In the “reward phase” (the third year to the end of the multiyear plan), countries receive a further $20 per additional child immunized (measured against the total number of children immunized the previous year with diphtheria-tetanus-pertussis vaccine, or DTP3). The second kind of support that GAVI offers is for new and underused vaccines. Countries can apply if they have a national coverage rate of 50% for the full infant course of DTP3. The specific new and underused vaccines available to eligible countries are hepatitis B, \textit{Haemophilus influenzae} type b, pneumococcal, and rotavirus vaccines. All 72 countries can apply for the yellow fever vaccine, regardless of DTP3 coverage rates. Countries that are eligible according to WHO criteria can also apply for measles vaccination (second dose). GAVI offers three other kinds of support, and all 72 countries can apply for these: injection safety support, health system strengthening, and civil society organization support.

Some critics have questioned whether GAVI’s focus on new and underutilized vaccines like hepatitis B is the best strategy. They have argued that GAVI’s priority should be on increasing the coverage of traditional EPI vaccines.\textsuperscript{55} Critics have also charged that, through its partnership with the private sector, GAVI is creating profitable new markets for multinational vaccine manufacturers for the more expensive vaccines such as hepatitis B vaccine (recombinant) and that GAVI has not been tough enough with these companies in negotiating prices.\textsuperscript{56} Godal, GAVI’s first executive secretary, rebuts these accusations as “nonsense,” stating, “If the public sector can work to help make the developing-country vaccine environment more attractive to vaccine manufacturers, children living in the poorest countries will have access to better and more effective vaccines.”\textsuperscript{57}

Critics have also charged that GAVI is making it difficult for developing countries to manufacture vaccines locally. They point out that GAVI has resisted requests by countries with generic-drug industries (including Brazil, India, and Indonesia) for supporting the transfer of patented vaccine technology.\textsuperscript{58} Respect
for intellectual property rights, however, was agreed on at the first GAVI Alliance Partners’ meeting in 2000 as a condition for developed country industry involvement. The GAVI Alliance supports the developing world vaccine industry through procurement of vaccines (if prequalified by WHO) and the allocation of one rotating seat on GAVI’s board. At the heart of these questions are concerns about the role of the private sector in global health partnerships and specific worries about sustainability, transparency, and accountability of public-private partnerships in health.

While these debates continued, GAVI made a significant impact on access to hepatitis B vaccine in developing countries through financing both the introduction of the vaccine and the infrastructure needed to support vaccination. GAVI’s activities especially affected the adoption and affordability of hepatitis B vaccine. As of June 2004, 85% of all countries with adequate delivery systems had introduced the hepatitis B vaccine into their routine systems (149 countries). In addition, 82% of the GAVI Fund–eligible countries with adequate delivery systems had introduced the vaccine into their routine systems (61 countries). Figure 4.1 shows that coverage with three doses of hepatitis B vaccine has risen steadily since 1990, reflecting increased national adoption into routine immunization programs and also growing coverage within some countries. Coverage levels in many countries remain low, however, and addressing this problem is a main challenge facing hepatitis B vaccine advocates.

Because prices of hepatitis B vaccine remain higher than the traditional EPI vaccines, continued access to the vaccine in developing countries depends on the sustainability of the GAVI model. In its first phase of operation (2000–2005), GAVI decided it would help a country introduce a new or underutilized vaccine such as hepatitis B for free for five years. The logic behind this approach was that during those five years, vaccine prices would decrease, and then developing country governments and donors would take on the financing of procurement. GAVI has found, however, that prices have not declined as expected (prices of combination vaccines with hepatitis B have in fact increased), countries are not able to afford procurement, and other donors have not stepped in to help. GAVI subsequently reformed its business model in order to support countries to gain long-term financial sustainability. This new model requires countries to co-pay for vaccine procurement from the beginning but does so over a longer time period than in its first phase to promote sustainability (GAVI’s second phase is from 2006–2015). A country’s level of co-pay depends on its ability to pay. Success of this new model will have a strong influence on creating access to the vaccine in developing countries in the short and medium term.
Conclusions

This story of access for the hepatitis B vaccine demonstrates the close linkages between architecture, availability, affordability, and adoption (see Table 4.4 for a summary of the access barriers and strategies). For decades, problems in affordability blocked access, as the price of hepatitis B vaccine remained too high for developing countries to include in their national immunization programs. As a result, demand outside of industrialized countries was low. Product adoption was also hampered by safety concerns about plasma vaccines and a limited understanding by global and national actors about the burden of hepatitis B in many countries. With low demand, manufacturers refused to increase production capacity for the vaccine, product prices remained high, and vaccine availability was limited.

New players in the architecture of hepatitis B vaccine successfully addressed the problem of limited availability, affordability, and adoption through several key...
strategies. The Task Force, an effective product champion for hepatitis B vaccine both at the global level and in developing countries, achieved decreases in the vaccine’s product prices by fostering competition and showing companies that a market for the vaccine existed in developing countries. But the Task Force also had limitations. Problems persisted of low national adoption in developing countries due to numerous pressing health problems and inadequate financing of hepatitis B vaccine for mass immunization programs. While the Children’s Vaccine Initiative tried in the 1990s to address these problems of access to underutilized vaccines like hepatitis B, this organization lacked sufficient political and financial power. These experiences show the importance of establishing a robust architecture for fulfilling access goals.

The establishment of the GAVI Alliance changed the architecture in ways that helped solve the problems of limited availability, affordability, and adoption. By financing the procurement of hepatitis B vaccine for developing countries through the GAVI Fund and forecasting demand across countries, GAVI showed vaccine producers that a viable international market for hepatitis B vaccine existed. GAVI’s actions also further facilitated the entry of new manufacturers, an increase in manufacturing capacity, a rise in price competition, and the creation of a steady vaccine supply. Giving industry a seat equal to UN agencies within GAVI’s board of directors created closer public-private collaboration. But this model also has its critics. They have argued that industry’s integral involvement in GAVI kept recombinant hepatitis B vaccine prices higher than necessary, thereby limiting access in poor countries and raising questions about long-term sustainability.

This case demonstrates several other factors that facilitated the entry of vaccine producers into the hepatitis B vaccine market. For instance, the Task Force’s role as a product champion helped to develop early relationships with several Korean companies and persuaded them of the growing demand for the vaccine in developing countries. In addition, work by WHO staff, government officials, and the vaccine industry to improve national drug regulating authorities and clinical testing capacities assisted the entry of vaccine producers with quality products. The expiry of patents also facilitated the entry of new manufacturers. Finally, the flow of global financing for immunization programs changed the calculus of affordability for countries. The financial support from the Bill & Melinda Gates Foundation and other donors made a huge difference in making the GAVI architecture effective. GAVI’s support for the procurement of vaccines and the strengthening of health systems in developing countries helped create the basis for improved access to hepatitis B vaccine around the world.
The global architecture of hepatitis B vaccine—involving the Task Force, WHO, and the GAVI Alliance—thus successfully addressed problems of limited availability, affordability, and adoption of this technology in developing countries. A major issue now is how to improve vaccination rates in countries with low coverage. Continuing access to the vaccine in the future also remains a major problem. Solving these problems will depend on whether national governments and donors continue to finance the vaccine and on related factors, including product price, the sustainability of GAVI, and government and donor funding priorities.

Table 4.4 | Hepatitis B vaccine access table

<table>
<thead>
<tr>
<th>BARRIER</th>
<th>STRATEGY</th>
<th>SPECIFIC ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of effective global product champion for developing countries</td>
<td>Identify effective leadership and design partnerships for the technology</td>
<td>Establishment of the International Task Force on Hepatitis B Immunization to address problems in availability, affordability, and adoption</td>
</tr>
<tr>
<td>Safety concerns for plasma vaccines (affecting national and end-user adoption)</td>
<td>Conduct safety evaluations that can be disseminated to policy makers and end-users</td>
<td>WHO conducted safety assessments of the plasma hepatitis B vaccine</td>
</tr>
<tr>
<td>Limited understanding of burden of disease for hepatitis B (affecting global and national adoption)</td>
<td>Facilitate international meetings that can promote consensus on the disease and the vaccine</td>
<td>Academic researchers and companies developed new hepatitis B vaccines using DNA-recombinant technology</td>
</tr>
<tr>
<td></td>
<td>Seek global recommendation on hepatitis B vaccine</td>
<td>The Task Force and WHO convened an international meeting to encourage the integration of hepatitis B vaccine into national immunization programs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WHO secured a World Health Assembly recommendation on the integration of hepatitis B vaccine into national immunization programs</td>
</tr>
</tbody>
</table>
### Table 4.4 | Hepatitis B vaccine access table (continued)

<table>
<thead>
<tr>
<th>BARRIER</th>
<th>STRATEGY</th>
<th>SPECIFIC ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AFFORDABILITY</strong></td>
<td>High product price (affecting government affordability)</td>
<td>Promote lower prices through expanded competition and entry of new manufacturers into the market</td>
</tr>
<tr>
<td><strong>AVAILABILITY</strong></td>
<td>Difficulties in producing large quantity of plasma vaccine because of need for blood from hepatitis B carriers Delivery challenges from weak immunization programs and problems in administering birth dose</td>
<td>Develop second generation of hepatitis B vaccine Show that delivery methods can be implemented effectively Support health system improvement</td>
</tr>
</tbody>
</table>

### Endnotes


Patlak.


Patlak.


Blumberg.

Muraskin, *The War Against Hepatitis B*.

Blumberg.

Muraskin, *The War Against Hepatitis B*.


DeRoeck.

Patlak.


Mahoney, “DNA Hepatitis B Vaccine.”

DeRoeck.


Vryheid et al.

Vryheid et al.


Vryheid et al.

Vryheid et al.

Muraskin, *The War Against Hepatitis B*. 

28 Muraskin, *The War Against Hepatitis B*.

29 Muraskin, *The War Against Hepatitis B*, 92.

30 Vryheid et al.

31 DeRoeck.

32 Muraskin, *The War Against Hepatitis B*.


34 Muraskin, *The War Against Hepatitis B*.

35 Kane.

36 Vryheid et al.

37 Muraskin, *The War Against Hepatitis B*.


39 UNICEF.

40 DeRoeck.

41 DeRoeck.

42 Mahoney, “Public-Private Partnerships”; and Mahoney, “DNA Hepatitis B Vaccine.”

43 Mahoney, “Public-Private Partnerships.”

44 Mahoney, “Public-Private Partnerships.”


47 Muraskin, “The Last Years of the CVI.”

48 Muraskin, “The Last Years of the CVI.”

49 Muraskin, “The Last Years of the CVI.”


51 Wittet.

53 Gates Foundation.

54 Gates Foundation.


58 Madhavi.

59 Gates Foundation.