

Case 20

Preventing Hib Disease in Chile and the Gambia

Geographic areas: Chile and the Gambia

Health condition: Researchers in Chile estimated that the incidence of *Haemophilus influenzae* type b (Hib) disease in Santiago during the late 1980s was 32 per 100,000 infants under 6 months of age, and 63 per 100,000 in infants aged 6 to 11 months. The proportion of children who died after contracting the disease was relatively high at 16 percent. In the Gambia, just over 200 children per 100,000 developed Hib meningitis in 1990.

Global importance of the health condition today: Worldwide, Hib disease is the leading cause of bacterial meningitis in children under 5 years of age and the second most common cause of bacterial pneumonia deaths in this age group. It kills an estimated 450,000 children every year and causes some 2 million cases of disease.

Intervention or program: Chile's Ministry of Health introduced the Hib vaccine into the routine immunization program for infants in 1996. The Gambia began administering the vaccine routinely as part of the national immunization program in 1997.

Cost and cost-effectiveness: The government of Chile has paid \$3.39 million for the combined DTP-Hib vaccine, a figure that represents nearly 23 percent of the total immunization budget and 0.7 percent of the government health expenditure. In Chile, the price per dose is \$3, and the government saves an estimated \$78 for each case of Hib prevented. Aventis Pasteur's donation of the vaccines in the Gambia helped make the immunizations possible there, and financial support from the Global Alliance for Vaccines and Immunization will help sustain the program through 2008.

Impact: The incidence of Hib meningitis in Chile fell by 91 percent and that of pneumonia and other forms of Hib disease fell by 80 percent following an initial trial in 36 health centers in 1994. The number of children developing Hib meningitis in the Gambia dropped almost ten-fold, from 200 per 100,000 to 21 per 100,000, in the 12-month period after the start of routine immunization. In the last two years of the study, there were just two cases.

Although it is a major cause of bacterial meningitis and pneumonia in young children worldwide,¹ the microbe *Haemophilus influenzae* type b (Hib) has avoided the notoriety of other major killers. Yet researchers have estimated that

it is responsible for the deaths of some 450,000 people worldwide and at least 2 million cases of disease each year.^{2,3} Hib meningitis is particularly lethal, killing 20 to 40 percent of the children who get it and leaving as many as half of the survivors with some lasting impairment, such as deafness or mental retardation.

The first draft of this case was prepared by Phyllida Brown.

Box 20–1

Conjugate Vaccines

Until the late 1980s the only available Hib vaccines were based on the polysaccharide, or sugary, capsule of the bacterium. These vaccines protected older children and adults but not young infants, who were at greatest risk of infection, because their immune systems did not respond well to the vaccines. The new generation of conjugate vaccines contain two components: the Hib polysaccharide capsule and, attached to it, a “carrier” protein antigen such as tetanus toxoid. This antigen stimulates a strong T-cell related immune response from the infant immune system. Several Hib conjugate vaccines have been licensed, including combinations with DTP and DTP plus hepatitis B.

In principle, most of this disease and suffering is avoidable. Since the late 1980s, highly effective vaccines against Hib have been licensed (see Box 20–1). Their impact in the industrialized countries, where they are widely available, has been dramatic. For example, in the United States, within four years of the initial licensing of conjugate vaccines in December 1987, the number of young children diagnosed with Hib disease fell by 71 percent, with up to 16,000 cases of the disease prevented in 1991 alone.⁴ Similarly, in the United Kingdom and Finland, Hib immunization resulted in as steep or even steeper declines in the incidence of the disease.^{5,6}

For most low- and middle-income countries, the relatively high cost of Hib vaccines (up to \$7.50 for three doses, compared with just a few cents for the basic vaccines such as diphtheria-tetanus-pertussis, or DTP) has kept them beyond reach (S. Jarrett, UNICEF supply division, personal communication, 2003). But, even with this cost, one study for the former Children’s Vaccine Initiative estimated that the Hib vaccine could be delivered as part of routine immunization in sub-Saharan Africa for just \$21 to \$22 per life-year saved.⁷ This makes it highly attractive to governments, given that anything costing less than \$25 per life-year saved is considered an excellent “buy.” However, governments of develop-

ing countries have been unable to take advantage of the potential, and because of this, one recent assessment concluded that Hib vaccines have merely dented the global burden of this disease, reducing the estimated number of cases per year by less than 40,000.²

Basics of Hib

The vast majority of Hib infections are in children under the age of 5 years of age. The age group at greatest risk of Hib meningitis globally is infants aged 6 to 11 months. In this group, the estimated annual incidence is 67 per 100,000.¹ After age 2, the risk of contracting Hib meningitis drops sharply. Overall, among children under 5 years, 23 per 100,000 develop Hib meningitis each year.

Infection patterns differ around the world; in sub-Saharan Africa the number of new cases in infants up to 11 months old is around 200 for every 100,000 infants, compared with some 60 per 100,000 in the Americas. Europe and Asia appear to have lower rates. Within each region, certain populations appear to have exceptionally high risks of Hib infection, including Navajo Indians and Alaskan Indians in the United States and Australian Aborigines.

On average, 14 percent of the children who develop Hib meningitis die, a measure known as the case fatality rate.¹ This is similar to the overall case fatality rate for severe acute respiratory syndrome (SARS), which the WHO (2002) estimates to be 15 percent. However, this global average for Hib meningitis masks sharp differences between wealthy and poor countries in children’s chances of surviving the disease. In industrialized countries, the case fatality rate is just 3.2 percent, because virtually all children who develop meningitis have access to emergency and adequate medical treatment. In developing countries overall, the case fatality rate is more than five times greater, at about 17 percent. In sub-Saharan Africa, where a high proportion of children lack access to specialized medical treatment, more than one in four affected children die, a case fatality rate of about 28 percent.¹ For every child who develops Hib meningitis in a given year, researchers estimate, about five children develop Hib pneumonia, making it the most common reason for death among those infected with this microbe.

The long-term impact on survivors of the disease is rarely taken into account in assessments of the social and economic costs of Hib. In the Gambia, only 55 percent of meningitis survivors fully recover; the rest may experience learning disabilities, neurological problems, deafness, and other major health and social problems.⁸ And treatment for Hib disease is becoming more complicated with the spread of antibiotic-resistant strains of the microbe.

All figures are approximate, because Hib pneumonia is relatively difficult to diagnose. Doctors typically do not establish exactly which microbes are responsible for a child's pneumonia before treating it. For this reason, also, case fatality rates for Hib pneumonia are more difficult to document than rates for Hib meningitis.

Researchers base their estimates of the incidence of Hib pneumonia on what proportion of all pneumonia cases are prevented when Hib vaccines are given. In both the Gambia and Chile, studies in the 1990s showed that mass Hib vaccination reduced the incidence of confirmed cases of pneumonia of all types by just over 20 percent,^{9,10} leading researchers to conclude that Hib is responsible for about a fifth of all severe pneumonia in children under 5 years of age in these two countries.

Chile: Evidence of Need and Public Demand

Chile has an average income per person of \$5,220,¹¹ a figure that puts it among middle-income nations. Its infrastructure is largely modern, and immunization services are efficient, with more than 95 percent of infants receiving routine vaccines.

Chile's first step toward introducing Hib vaccine came in the late 1980s, when researchers at the Ministry of Health first estimated the incidence of Hib disease in the Santiago area and concluded that it was an important public health problem.¹² Until this point, there had been no information about the extent of the disease in Chile. The researchers analyzed clinical and laboratory records between 1985 and 1987 at all seven government hospitals in the Santiago area. They matched these data with census records to estimate the incidence of Hib in the Santiago population of children under 5 years, which was estimated at 500,000 at that time. During the study

period they identified 343 cases of laboratory-confirmed Hib disease, including 242 cases of meningitis; the remainder were other forms of invasive Hib disease—that is, Hib pneumonia, Hib bacteremia, and other severe forms of the disease. The peak age for infection was between 6 and 11 months, with the risk rapidly reducing after infants passed their first birthday.

At first glance, the figures suggested that the incidence of Hib was only about half as high as in infants in the United States at the same time. However, there were strong reasons to believe that the figures underestimated the true extent of Hib disease in Chile. Dr. Rosanna Lagos, a pediatrician at the Center for Vaccine Development in Santiago and an expert in Hib, explains that the team found sharp variation between hospitals in the rates at which bacteria from patients' samples were successfully detected and cultured in the laboratory. The process of isolating and culturing bacteria is difficult and depends on the specialist skills and capacity of the laboratory and its staff. In the northern area of the city, where the local hospital had a specialist interested in Hib, the rate of detection was twice as high as in the rest of the city. The researchers assumed that the specialist's estimate was likely to be more accurate and on this basis estimated that the annual incidence of Hib meningitis in the Santiago area was 32 per 100,000 in infants aged five months and under, and 63 per 100,000 in infants aged 6 to 11 months.^{12,13} These figures are comparable with those in other temperate industrialized countries where Hib was endemic before immunization.

In addition to indicating that Hib was a widespread problem in Chile, the study also revealed that the proportion of children who died after contracting Hib disease in Santiago was relatively high, at 16 percent. (In industrialized countries the case fatality rate is below 4 percent.) The researchers reasoned that outside the city, where access to hospital treatment would likely be less widespread, the chances of death would be equal or greater.

Assessing the Feasibility and Effectiveness of National Hib Immunization

Although two Hib conjugate vaccines were licensed in Chile in 1992, they were not initially introduced into the

country's routine immunization system. Their licensure had been based on evidence of their *efficacy*—their biological protective effect—in controlled trials in the industrialized countries. In Chile, however, the Ministry of Health had not been convinced that the high costs of the vaccine would justify its routine use. Once the disease burden had been shown to be significant, however, the ministry agreed in 1994 that researchers should further explore the use of the Hib vaccine.¹³ Rather than performing a randomized clinical trial of the vaccine's efficacy in controlled conditions, the researchers did what is known as an “intent-to-vaccinate” study. This observed the *effectiveness* of the vaccine—its impact on a large population of infants receiving it in the normal conditions of a routine immunization service. Thirty-six primary health centers in Santiago were enrolled for the study and administered the vaccine with other routine immunizations for a year. The researchers assumed that some children would fail to turn up for immunization and that some would receive only one or two of the three required doses. For a comparison group, they observed children in 35 additional centers in the city where Hib vaccine would not be offered.

To minimize the number of shots for children and to increase cost-effectiveness, the researchers tested a combination of Hib conjugate vaccine and the established DTP antigens in the same syringe. In the 35 centers that did not receive Hib, children received only DTP as usual. The total number of children involved was more than 70,000. The vaccine for the large-scale study was donated by the manufacturer, Pasteur Mérieux Serums et Vaccins of France, now Sanofi Pasteur; additional external support for the studies came from the US National Institute of Allergy and Infectious Diseases.

Hib Disease Falls 90 Percent in a Year

The results of the study were dramatic. Researchers compared the number of new cases of Hib meningitis and pneumonia diagnosed during the study period in the two groups of health centers. Among the children in the health centers where Hib vaccine was available, the number of meningitis cases was reduced by 91, and the number of cases of pneumonia and other forms of Hib disease were reduced by 80 percent, compared with children in the DTP-only centers.¹⁴

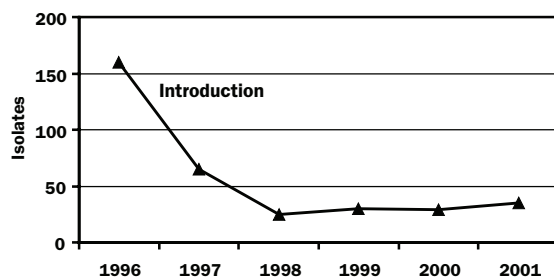
The vaccine had won its case. Not only was it effective but also feasible and practical for health centers to combine DTP and Hib vaccines and deliver them within the routine system. “At this point, the Ministry of Health decided that it was a good moment to do it,” says Lagos. The ministry introduced the vaccine into the routine immunization program for babies throughout Chile, starting in July 1996 (see Figure 20–1).

Affordability, Sustainability, and Public Demand

Although the Chilean government's decision was based on the public health evidence, there was also a strong public demand for immunization against meningitis. The government faced a complex situation. Dr. Fernando Muñoz of the Ministry of Health explains that before the vaccine was introduced into the national immunization program, it was already being recommended and administered by private pediatricians to families who could afford to pay. “The national program was facing the need to solve this equity failure,” he says.

An entirely different political problem had emerged at the same time. Chile had recently suffered from outbreaks of a different type of meningitis, meningococcus type B. A private laboratory producing a vaccine against meningococcus type B was lobbying for its product to be introduced, and the media picked up and ran with the campaign. However, the evidence for the vaccine's

Figure 20–1
Impact of Hib vaccination.



Source: Pan American Health Organization. “Monitoreo de las enfermedades causadas por Hib: Post-introducción de las vacunas.” Presentation: XV Meeting of the Technical Advisory Group on Vaccine-preventable Diseases. Washington, DC: PAHO; 2002.

efficacy in infants and toddlers was not convincing, says Muñoz. “The ministry faced a dilemma.” By introducing the Hib vaccine, the government managed to offer the public something that was useful, albeit against a different form of meningitis, instead of a vaccine of questionable efficacy. While Hib meningitis had a lower popular profile than meningococcal meningitis, its burden was now known to be substantial, and it did at least have a vaccine that had proved itself in rigorous trials. Demand for the vaccine against meningococcus type B gradually faded, says Muñoz.

National pride also played a part. The fact that Uruguay had introduced the Hib vaccine two years earlier spurred action in Chile. “The Chilean program of immunizations is seen in Chile as one of the great achievements of Chilean public health,” says Muñoz. “We have always seen ourselves as pioneers in the field, and it is hard to accept losing leadership in the region.”

The cost of the vaccine was initially substantial, accounting for about half of the total immunization program, but the government funded it in full with public funds from general taxes. By 2003, that figure had fallen: The ministry was paying \$3.39 million for the combined DTP-Hib vaccine, or 22.9 percent of the total immunization budget, which was approximately 0.7 percent of government health expenditure. The price per Hib dose dropped from around \$15 in 1996 to around \$3 in 2003 (F. Muñoz, personal communication, Chilean Ministry of Health, December 2, 2003). And in 1998, researchers concluded that the nation would save \$78 for every case of Hib prevented, providing further evidence to support the public expenditure.¹³ “Under Chilean regulations, EPI [Expanded Programme on Immunization] vaccines are considered as public goods and are provided free of charge to all the population,” he says.

The Gambia: An Investment Against Poverty

The Gambia is among the poorest countries, with an average annual income of \$280 per person.¹¹ It is starkly different than Chile, with a much less developed infrastructure. For example, the country has about seven telephone lines per 100 people compared with almost 60 in Chile.¹⁵ However, the country’s immunization coverage—the proportion of all children immunized

with basic vaccines such as DTP—is relatively high, at 85 percent, compared with many sub-Saharan African countries,⁸ and it spends a higher proportion of its gross domestic product on health, approximately 3 percent, than many other low-income countries.

Better primary health care has substantially reduced infant mortality, but it remains high at 90 per 1,000 live births, based on 2001 figures.¹⁵ This is twice as high as in South Africa, although well below the levels of some other very poor African countries such as Niger (about 190 per 1,000 live births) or Mali (about 150 per 1,000 live births).

Although Gambians’ access to health care has improved, many people still walk several kilometers to the nearest health facility, and 10 percent of the population lives more than 7.5 kilometers from any facility. There are only four doctors for every 100,000 people, compared with 15 in Nigeria and more than 150 in China.¹⁵ The Gambian government also acknowledges disparities between its regions in access to health care, particularly in the eastern, upriver part of the country, and that “underfunding of the health sector persist[s] at all levels.”¹⁶

Many children are brought to clinics for immunization later than the recommended visits at two, three, and four months. “This is an important factor,” says Dr. Richard Adegbola of the Medical Research Council Laboratories in Fajara, the Gambia. The age at which infants are most likely to become infected with Hib appears earlier in Africa than in higher-income settings such as the Americas; therefore, even slightly late vaccination puts children at very high risk of infection (R. Adegbola, personal communication, Medical Research Council Laboratories, June 2003).

Since 1990, the Gambia’s health system has performed continuous surveillance of its infant population for Hib disease in the country’s western region, where clinic, hospital, and laboratory facilities are adequate to effectively accomplish the task. In 1990, just over 200 children per 100,000 developed Hib meningitis each year.⁹ Here, Hib struck younger, more seriously, and more frequently than in more developed countries: less than half of patients make a full recovery from Hib disease in the Gambia, and a third of those that developed Hib meningitis died.¹⁷

New awareness of the scale of the Hib burden led the government and its international partners to take action. Between 1993 and 1995, researchers conducted a large, controlled trial of the Hib vaccine, involving 42,000 infants and requiring the participation of the three main hospitals and the health laboratories in the Gambia's western region. The trial used vaccine donated by its manufacturer Aventis Pasteur and was supported by a range of partners including the US Agency for International Development, WHO, UNICEF, the staff of the UK Medical Research Council, and others. Children were allocated at random to receive either DTP plus Hib vaccine or DTP alone. During the trial, and for up to 36 months afterward, all children with symptoms of invasive Hib disease (mainly meningitis and septicemia) were examined carefully with laboratory tests to culture bacteria, with lumbar punctures, blood tests, and chest X-rays as appropriate.

If any researchers expected the vaccine to produce a less dramatic effect in the Gambia than in an industrialized country, they were wrong. Compared with the children who received no Hib vaccine, the Hib-vaccinated group had 95 percent fewer cases of invasive Hib disease, confirming that the vaccine was as highly protective as in industrialized countries. The trial was also key in demonstrating the impact of the vaccine in reducing all types of pneumonia in Gambian infants by 21 percent, and a 60 percent protection against carriage in the child's second year.¹⁷ As a result of the study, Dr. Kim Mulholland and his colleagues concluded that "the introduction of Hib vaccines into developing countries should substantially reduce childhood mortality from pneumonia and meningitis."⁹

From Clinical Trial to Messier Reality

The logical next step, then, was to introduce the vaccine into the national immunization program. However, cost was a major obstacle. Total expenditure on health in the Gambia is only \$13 per person each year, with the government spending \$6 per person and external funding and households contributing the remaining \$7. And it costs \$37 to fully immunize a child in the Gambia.^{18,19} For at least the short- to medium-term, external support was needed to extend the benefits of the vaccine that the trial participants had enjoyed to the rest of the popula-

tion—and to maintain those benefits for the participants' families.

A key question was whether the vaccine would work as well in real-life Gambian conditions as in a clinical trial. As in other low-income countries, health services in the Gambia struggle with interruptions in the vaccination supply chain, breakdown of refrigerators, and staff shortages, all of which can interfere with the delivery of immunization. Plus, the lack of coordination among funding sources can cause resources to be wasted; for some years, the program had in stock 14 ice-lined refrigerators, five refrigerators, six freezer-refrigerators, and one freezer—but none were in use.¹⁹ Although the Gambia has invested considerable effort in improving its vaccine cold chain with the use of solar power and decentralizing vaccine storage and health care management to get vaccines where they are needed in a timely fashion,¹⁶ the system is far from perfect. Researchers and health officials decided to perform a large-scale, long-range study of its effectiveness.

In 1997, an agreement was signed between the prime minister of the Gambia and Aventis Pasteur to carry out the study, involving the population of the country's western region, where about half the country's 1 million inhabitants live. Aventis Pasteur donated the vaccine for a five-year period. Between May 1997 and April 2002, the vaccine was administered routinely as part of the national EPI program, with continuous surveillance for cases of Hib disease. The study was conducted by Adegbola and others at the Medical Research Council Laboratories in Fajara, the Gambia, together with colleagues at the Gambian Ministry of Health, the Royal Victoria Hospital in Banjul, and the WHO. An interim report was published in 1999,⁸ and the final results have now been reported to the WHO.²⁰

Saving Lives

Adegbola and his colleagues have watched Hib virtually disappear. The number of children developing Hib meningitis dropped almost ten-fold, from 200 per 100,000 to 21 per 100,000 in the 12-month period after the start of routine immunization. By the fifth year after routine immunization began, this incidence was reduced to zero.¹⁷ Of the rapidly dwindling numbers of children

who did develop the disease—fewer than 50—more than half had not been vaccinated, while all but two of the remainder had received incomplete immunization of just one or two doses. In the last two years of the study, there were just two cases; no cases have been reported in western Gambia since 2002.¹⁷ Two doses of the vaccine demonstrated a 94 percent efficacy. The results demonstrate that this vaccine can be highly effective even in an impoverished country where the health system faces numerous logistic and financial challenges.

Equally important, says Adegbola, the vaccine appears to stop children from carrying Hib bacteria in their noses and throats and therefore reduces the transmission of the microbe from one person to another. Before the study, about 10 percent of children were Hib “carriers,” but with the introduction of the vaccine this figure has dropped to less than 1 percent (R. Adegbola, personal communication, June 2003). This is particularly significant given the delays in immunizing some infants because the reduced transmission helps create herd immunity. “Even if children don’t receive the vaccine at the time they are most susceptible, this [reduced carriage] tends to have an [additional] effect,” says Adegbola.

Adegbola and colleagues note that the Gambia’s success in virtually eliminating Hib disease was achieved even despite an irregular vaccine supply marked by periodic interruptions. Fewer than 70 percent of children completed the full schedule of immunizations and many of the vaccine doses were late. Thus, the country’s experience provides encouraging evidence that Hib elimination can be achieved in other developing countries with strong but imperfect immunization delivery. With even modest immunization coverage and suboptimal conditions, all children can benefit.

Another Five Years

The agreement with Aventis Pasteur to provide free vaccine has now run its course. However, the Gambian government is able to continue providing Hib immunization to all children nationwide for at least five more years, starting in 2003. This is due to support from the Global Alliance for Vaccines and Immunization (GAVI), a partnership set up in 2000 between governments and their international partners, including WHO, UNICEF, the World Bank, the Bill & Melinda Gates Foundation,

and the vaccine industry. GAVI supports low-income countries to improve access to vaccines against major killers, including new and underused vaccines such as Hib and hepatitis B, by buying vaccines and investing in improved immunization services. In the longer term, the alliance seeks to enable governments to mobilize new resources for immunization from within their own budgets and from other sources, so that they can provide sustainable services.

Other Low-Income Countries Adopt Hib Vaccine

Other developing countries are now using the Hib vaccine. Most countries in Latin America and the Caribbean include the Hib vaccine as part of their routine EPI, thanks in part to the successful experiences of Chile and Uruguay, and the initial technical and financial support of the Pan American Health Organization in 1997 and 1998. Researchers concluded that the benefits of introducing Hib vaccine in the Cape Town area alone exceeded the costs of treating the disease by up to \$500,000.²¹ So, in 1999 South Africa started to include Hib immunization as part of its national program. With a major international effort and financial and technical support from the partners in GAVI, 10 additional low-income countries introduced Hib immunization in 2003 and 2004, providing protection for an additional 4 million children in total each year. Results are encouraging: A recent study demonstrated that three years after Kenya introduced Hib vaccine into its routine immunization program, rates of the disease were down 88 percent, preventing more than 3,000 hospitalizations per year.²² By 2007, the vaccine will be introduced in several additional Asian countries, including Malaysia, Mongolia, and Sri Lanka, where the disease burden has recently shown to be higher than previously expected.²³

The final chapter in the Hib story is not yet written. Whether large numbers of developing countries where Hib disease is a major problem will choose to introduce and sustain the use of the vaccine is not yet known. It depends in part on how and whether financing is made available—and how expensive the vaccine is over the medium term. The health impact in regions of the world where Hib vaccine has not yet been used on a large scale is also unknown, and researchers are following closely to see whether the positive experiences now being consoli-

dated in Latin America and the Caribbean, and parts of Africa, will be shared elsewhere.

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