Chapter 20

Vaccine-Preventable Diseases

Logan Brenzel, Lara J. Wolfson, Julia Fox-Rushby, Mark Miller, and Neal A. Halsey

Vaccination against childhood communicable diseases through the Expanded Program on Immunization (EPI) is one of the most cost-effective public health interventions available (UNICEF 2002; World Bank 1993). By reducing mortality and morbidity, vaccination can contribute substantially to achieving the Millennium Development Goal of reducing the mortality rate among children under five by two-thirds between 1990 and 2015. Accelerated research into the development of new vaccines has been made possible in part by innovative public-private partnerships, such as the Global Alliance for Vaccines and Immunization (GAVI). GAVI focuses on expanding access by immunization programs in developing countries to new and underused vaccines, such as those for hepatitis B and *Haemophilus influenzae* type B (Hib). These newer, more expensive vaccines are challenging previous notions of the cost-effectiveness of immunization. Analyses of their costs and cost-effectiveness are particularly important because of the need to determine the level of resources required in the future to improve immunization programs, to cover the costs of new vaccines, and to allocate scarce public and external resources available for immunization in the most optimal manner.

This chapter analyzes the costs and cost-effectiveness of scaling up the EPI and introducing selected new vaccines into the program. It also summarizes the epidemiology of diseases preventable through immunization and estimates the disease burden with and without immunization programs. In addition, the chapter discusses the organization, delivery, and financing of immunization programs and highlights future prospects and areas for further study.

Several areas overlap with other chapters. For example, the vaccines that prevent measles, tuberculosis, diphtheria, pertussis, Hib, and *Neisseria meningitis* prevent respiratory diseases. Some vaccines, such as those against measles and pertussis, prevent diseases that cause or contribute to malnutrition. Chapter 16 provides an in-depth review of tuberculosis and a discussion of the potential impact of bacillus Calmette-Guérin (BCG) vaccines. This chapter also does not discuss some new vaccines, including conjugate *Streptococcus pneumoniae*, influenza, typhoid fever, and rotavirus, because other chapters deal with those diseases and vaccines. Vaccines to prevent mumps and varicella that are routinely used in some developed countries are not included in most vaccination programs in developing countries. Other interventions that can reduce the burden of vaccine-preventable diseases and are not covered in this chapter include clean umbilical cord care to reduce the incidence of neonatal tetanus, vitamin A therapy to reduce the case-fatality rate (CFR) from measles, and intensive clinical care that can reduce the mortality associated with most of the vaccine-preventable diseases.

CAUSES AND EPIDEMIOLOGY OF DISEASES PREVENTED BY VACCINES USED IN NATIONAL IMMUNIZATION PROGRAMS

The epidemiology and burden of vaccine-preventable diseases vary by country and region partly because of differences in vaccine uptake. Numerous other factors that contribute to the disease burden include geography, seasonal patterns, crowding, nutritional status, travel to and from other countries, and possibly genetic differences in populations that affect disease severity. Table 20.1 summarizes the features of selected vaccines

Table 20.1 Selected Vaccine-Preventable Diseases and Vaccines

Category	Tuberculosis	Diphtheria	Tetanus	Pertussis	Poliomyelitis	Measles[a]	Rubella	Hib	Hepatitis B	Yellow fever	Meningococcal disease	Japanese encephalitis
Causative agent	Mycobacterium tuberculosis	Toxin-producing bacterium (*Corynebacterium diphtheriae*)	Toxin-producing bacterium (*Clostridium tetani*)	Bacterium *(Bordetella pertussis*)	Virus (serotypes 1, 2, and 3)	Virus	Virus	Bacterium (*Haemophilus influenzae* type B)	Virus	Virus	*Neisseria meningitis* groups A, B, C, Y, W135	Virus
Reservoir	Humans (some bovine)	Humans	Animal intestines; soil	Humans	Humans	Humans	Humans	Humans	Humans	Monkeys and humans	Humans	Birds and mammals
Spread	Airborne droplet nuclei from sputum-positive persons	Close respiratory or cutaneous contact	Spores enter the body through wounds or the umbilical cord stump	Close respiratory contact	Fecal-oral; close respiratory contact	Close respiratory contact and aerosolized droplets	Close respiratory contact and aerosolized droplets	Close respiratory contact	Blood, perinatal, household, occupational, or sexual transmission	Bites by infected mosquitoes	Close respiratory contact	Bites by infected mosquitoes
Transmission period	As long as sputum acid-fast bacilli are positive	Usually under two weeks; some chronic carriers	No person-to-person transmission	Usually under three weeks (starts before cough is apparent)	A few days before and after acute symptoms	Four days before rash until two days afterward	A few days before to seven days after rash; up to one year of age in congenitally infected	Chronic carriage for months	Up to lifelong chronic carriage and transmission	Infected individuals can transmit the disease when bitten by a mosquito vector during the viremic phase (the first three or four days of illness)	Chronic carriage for months	Unknown, rare cases for several months
Subclinical infection	Common but not important in transmission	Common	No	Mild illness common: may not be diagnosed	More than 100 subclinical infections for each paralytic case	May occur in children under one, but relative importance is minimal	Common	Common	Common, especially in infants	Common	Common	Common
Duration of natural immunity	Not known; reactivation of old infection commonly causes disease	Lasting protective immunity not produced by infection; second attack possible	Lasting protective immunity not produced by infection; second attack possible	Incomplete and waning protection	Lifelong type-specific immunity	Lifelong	Lifelong	Uncertain; no protection against carriage and those previously infected may develop some disease (epiglottitis)	If develops, lifelong	Lifelong	Uncertain; no protection against carriage	Lifelong

Risk factors for infection (for unvaccinated individuals)	High population densities in regions with historically poor control; low socioeconomic status; poor access to care; immunodeficiency; malnutrition; alcoholism; diabetes	Crowding; low socioeconomic status	Wound contaminated by soil; umbilical cord; agricultural work	Young age; crowding	Poor environmental hygiene and sanitation	Highly transmissible agent with nearly 100 percent infectivity except for isolated populations; crowding, low socioeconomic status	Highly transmissible; crowding; low socioeconomic status	Failure to breastfeed; crowding; low socioeconomic status; immune deficiency, including HIV	Carrier mother, sibling, or sex partner; multiple sex partners; intravenous drug use; unsafe injection practices	Young age; forest workers; season (late rainy season, early dry season)	Crowding; respiratory viral infections, especially influenza	Young age; forest workers; season
Case-fatality rate[b]	See chapter 16	2 to 20 percent	25 to 90 percent	Up to 10 percent in infants and children	2 to 10 percent	0.05 to 10.0 percent	Less than 0.1 percent	Meningitis, 5 to 90 percent; pneumonia 5 to 25 percent	Acute, more than 1 percent; chronic; 25 percent (delayed)	10 to 40 percent	Untreated 90 to 100 percent; treated 5 to 20 percent	5 to 30 percent
Vaccine (number of doses); route	BCG attenuated *Mycobacterium bovis* (1); intradermal	Diphtheria toxoid (three to five primary including booster doses in most countries); intramuscular	Tetanus toxoid (three to five in children, including booster doses in many countries; five for women of childbearing age; adult boosters for injury prevention); intramuscular	Killed whole-cell or acellular pertussis (three to five, including booster doses in most countries); intramuscular	Live (OPV) (three to four primary plus campaigns);[c] killed (IPV) (three to four)	Measles (two); subcutaneous	Rubella (one or two); subcutaneous	Capsular polysaccharide linked to protein Hib (three to five); intramuscular	Hepatitis B surface antigen (three to four); intramuscular	Yellow fever attenuated live virus (1 plus boosters); subcutaneous	Vaccines for A, C, Y, W135 only; unconjugated polysaccharides given subcutaneously or intramuscularly: one dose with repeat three to five years later for high-risk persons; conjugated: for C only or A, C, Y, + W135, one dose given intramuscularly	Live attenuated (two, China only); killed (two); booster commonly used but of uncertain value
Vaccine efficacy	0 to 80 percent for pulmonary tuberculosis; 75 to 86 percent for meningitis and miliary tuberculosis	More than 87 percent	More than 95 percent (more than 80 percent after two doses) in infants	70 to 90 percent	OPV: more than 95 percent in industrial countries; 72 to 98 percent in developing countries; lower protection against type 3 than 1 and 2; IPV: more than 95 percent	95 percent at 12 months of age; 85 percent at 9 months of age from one dose, more than 98 percent from two doses	95 percent (at 12 months and up)	More than 95 percent for invasive disease	75 to 95 percent; efficacy against chronic infection in infants born to carrier mothers; more than 95 percent for exposure at older ages	90 to 98 percent	Unconjugated polysaccharides: poor efficacy under two years of age; conjugated polysaccharides: approximately 95 percent and up serogroup specific	Live attenuated: 90 percent (after one dose at one year); 94 to 100 percent (after two doses one to two months apart); inactivated: 80 percent (declining to 55 percent after one year; no decrease in another study)

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Table 20.1 Continued

Category	Tuberculosis	Diphtheria	Tetanus	Pertussis	Poliomyelitis	Measles[a]	Rubella	Hib	Hepatitis B	Yellow fever	Meningococcal disease	Japanese encephalitis
Duration of immunity after primary series	Unknown; some evidence that immunity wanes with time	Variable: probably around five years; longer in presence of natural boosting or booster doses	10 years or more	Unknown; wanes with time	Presumed lifelong for both OPV and IPV, but unknown	Lifelong in most; rare cases of waning immunity after one dose, not two	Lifelong in most; presumed rare cases of waning immunity after one dose, not two	Unknown, but lasts for at least three years beyond period of greatest exposure	More than 15 years; further follow-up is continuing	For at least 10 years and possibly for life	Unconjugated wanes rapidly for children under five, more than three to five years for older children; conjugated uncertain	Unknown, may be lifelong
Schedule	Given at or near birth in populations at high risk	Three-dose schedule recommended at 6, 10, and 14 weeks in developing countries for DTP vaccine; other schedules in common use; booster doses at 18 months and four to six years also suggested	Normally given as DTP vaccine to children; unimmunized pregnant women should be given two doses of tetanus toxoid or tetanus-reduced diphtheria toxoid, and a total of five doses is required to provide protection through all childbearing years	Usually given in childhood as combination vaccine (DTP)	OPV: four doses (birth, 6, 10, and 14 weeks) in polio-endemic countries; birth dose may be omitted elsewhere with fourth dose given later; supplemental doses (up to 10) given in national campaigns for eradication; IPV: three to four doses: 2, 4, 6 to 18 months, and four to six years	First dose at 9 or 12 to 15 months); a second opportunity to receive a dose of measles vaccine (either through routine [18 months or four to six years] or supplemental immunization activities) should be provided for all children	First dose at 12 to 15 months; when given, a second dose with measles vaccine	Three or four doses; usually given during the same visit as for DTP	Several schedules: at birth, 6, and 14 weeks; with first three doses of DTP; birth dose needed if mother is a carrier and recommended if perinatal transmission of hepatitis B is frequent; four doses total can be given although only three are required	One dose at 9 to 12 months with measles in countries where yellow fever poses a risk	Unconjugated: one dose at two years or older and second dose three to five years later for high risk; conjugate C: three doses at two, three, and four or two, four, and six months for infants; one dose for older children and adults; conjugate A, C, Y, W135 currently only approved for one dose at 11 years or older	Live: one year and two years; killed: days 0, 7, and 30 followed by booster two years later and then every three years

Status as of the end of 2001	158 countries using BCG; 85 percent coverage	All countries; 78 percent coverage	Childhood: all countries; 78 percent coverage	All countries; 78 percent coverage	All countries; 79 percent routine, plus supplemental coverage	Routine first dose all countries, 77 percent coverage; second opportunity, 164 out of 192 countries	110 countries in 2003	89 countries; global coverage less than 18 percent	147 countries; global coverage 42 percent	29 of 43 countries at risk using vaccine; 30 percent coverage in target population	European countries, Canada (and United States in 2005)	Southeast Asia
Comments	Reasons for varying efficacy are multifactorial, including differences in vaccines	Recent trends to lower antibody levels in adults without booster doses because of waning immunity and less natural boosting	Five doses in adults provide protection for more than 20 years	Variability in whole cell vaccines; acellular vaccines used in some developed countries	Primary series gives incomplete protection in developing countries	Lower efficacy when maternal antibody present	Lower efficacy when maternal antibody present	None	Efficacy lower if injected into fat	None	None	None

Sources: WHO 2002, 2004.

DTP = diphtheria-tetanus-pertussis; IPV = inactivated polio vaccine; OPV = oral polio vaccine.

a. Measles vaccine is given as measles, measles-rubella, or measles-mumps-rubella vaccine. The latter two vaccines are routinely used in industrial countries and are increasingly being adopted in other countries. The World Health Organization recommends that the combination measles-rubella or measles-mumps-rubella vaccines be introduced only after careful evaluation of public health priorities within each country and following the establishment of an adequate program for measles control as demonstrated by high coverage rates as part of a well-functioning childhood immunization program.

b. Note that variations in case-fatality rates are related to access to care, type of care administered, setting, age at onset of disease, and other factors. The ranges presented in this table reflect both uncertainty as to actual case-fatality rates and the variability of populations.

c. As of 2003, an injected IPV is given alone or in combination with OPV in 31 countries. IPV is currently not recommended for routine use in developing countries because of its relatively high cost and uncertain efficacy when given at 6, 10, and 14 weeks. The usual recommended IPV schedule is 2, 4, and 6 to 18 months. Routine use of OPV is expected to cease following polio eradication. Stockpiles of monovalent OPV for each of the three virus types are under development to protect against vaccine-associated paralytic poliomyelitis and outbreaks of circulating vaccine-derived polioviruses.

in use in childhood immunization programs throughout the world.

Burden of Vaccine-Preventable Diseases

A number of vaccine-preventable diseases are not reportable events in many countries. The estimates of the burden of disease by the World Health Organization (WHO) are based on a combination of often incomplete vital registration data, mortality survey data, and mathematical models using numerous assumptions. Most models of vaccine-preventable diseases are derived from the susceptible fraction of the population (calculated from natural immunity from presumed historical infections in regions without previous vaccination and historical immunization coverage rates), infectivity rates of disease, sequelae of diseases, and estimates of local CFRs. The degree of accuracy of these models is only as good as the data supporting the assumptions. The disease burden is most appropriately represented by a range of values reflecting uncertainty. In this chapter, we estimate the burden of disease as the number of deaths and DALYs per World Bank region in 2001. The following description draws in part on discussion of methods for burden of disease calculations reflected in the Global Immunization and Vision Strategy of WHO and the United Nations Children's Fund (UNICEF) (Wolfson and Lydon 2005).

Diphtheria

Diphtheria is caused by a toxin-producing strain of the bacterium *Corynebacterium diphtheriae*, which is transmitted by means of respiratory droplets. The 2001 WHO estimates of diphtheria mortality are extrapolations from reported deaths in countries with full or partial vital registration systems.

Before the widespread use of immunization, more than 5 percent of people living in temperate climates suffered from clinical diphtheria at some point during their lifetimes (Griffith 1979). Rates exceeding 100 cases per 100,000 population were seen in Europe during World War II (Galazka, Robertson, and Oblapenko 1995). The CFRs from respiratory tract diphtheria have been 2 to 20 percent, with an average of 10 percent for patients receiving good medical care (Feigin, Stechenberg, and Hertel 2004). To estimate diphtheria deaths in the absence of vaccination and to project future deaths with and without vaccination, we assumed an average incidence rate of 15 per 100,000 and CFRs of 2.5 percent in developed countries, 5.0 percent in Europe and Central Asia, and 10.0 percent elsewhere (Birmingham and Stein 2003; Galazka and Robertson forthcoming).

Tetanus

Clostridium tetani is maintained in nature and is found in all countries. Spores remain viable for many years in soil and dust, especially in areas contaminated by animal feces (Cherry and Harrison 2004). The organism is usually transmitted through burns, cuts, and other penetrating injuries. Neonatal tetanus is the most common presentation in developing countries. The portal of entry is usually the umbilical stump but has been associated with circumcision and other surgical procedures (Birmingham and others 2004; Stanfield and Galazka 1984). Children born to women who do not have protective levels of tetanus antibody are susceptible to neonatal tetanus.

The estimated burden of neonatal tetanus assumes that in areas with low rates of skilled delivery, all births not protected by the immunization of pregnant women are subject to a preimmunization era neonatal tetanus mortality rate expressed as deaths per 1,000 live births (Birmingham and others 2004; Griffiths and others 2004). In other areas, we assume that births not protected through immunization or skilled delivery are subject to an incidence and CFR equal to 25 percent of the preimmunization era neonatal tetanus mortality rate.[1]

CFRs are directly associated with the quality of medical care available. With the availability of secondary and tertiary care, CFRs have declined to 25 percent or less (Cherry and Harrison 2004; Wassilak and others 2004). The CFRs used to derive cases from estimated deaths range from 40 percent in developed countries to 80 percent in the poorest developing countries. We estimate the tetanus burden other than for neonates by applying an estimated age distribution of total tetanus to the estimated neonatal tetanus deaths (Galazka and others forthcoming) and region-specific CFRs, which indicate a range of from 27 percent among children age one to four in developed countries to 65 percent among those age 80 or older in developing countries.

Pertussis

Bordetella pertussis is transmitted through respiratory excretions and occurs throughout the world. Most pertussis in developing countries occurs in school-age children. In developed countries, mild or asymptomatic infections in adults are believed to be common sources of transmission to very young infants (Edwards and Decker 2004). Clinical manifestations include an initial 7 to 10 days of rhinorrhea progressing to a cough that becomes paroxysmal or spasmodic, usually associated with profuse rhinorrhea (Cherry and Heininger 2004). Clinical pneumonia is seen in approximately 10 percent of infants.

Our estimates for the burden of pertussis followed the model described in Crowcroft and others (2003). We estimated that the proportion of susceptible children becoming infected in countries with vaccination coverage of less than 70 percent over the previous five years was 30 percent by age 1, 80 percent by age 5, and 100 percent by age 15. For countries with coverage of more than 70 percent in the past five years, we assumed

that 10 percent of susceptible children were infected by age 1, 60 percent by age 5, and 100 percent by age 15. A vaccine efficacy of 80 percent was assumed for preventing infection and 95 percent for preventing deaths. The CFR was 0.20 percent in infants, 0.04 percent in children age one to four, and 0 percent in those older than five in low-mortality countries; and 3.7 percent among infants, 1 percent among children age one to four, and 0 percent in those older than five in high-mortality countries.

Poliomyelitis

Before the availability of polio vaccines, as many as 90 percent of children in the developing world were infected with all three types of the polio virus in the first two or three years of life (Sutter and Kew 2004). In developed countries, transmission occurred primarily in school-age children and more than 90 percent of infections were asymptomatic; 4 to 8 percent of children had nonspecific febrile illness and less than 1 percent developed acute flaccid paralysis (Sutter and Kew 2004).

Children with residual paralysis require rehabilitation. Surgical intervention is necessary if contractures develop because of the lack of rehabilitative services following the acute illness. These children are at increased risk of premature death because of late onset postpolio muscle atrophy (postpolio syndrome), which occurs 20 to 40 or more years after acute illness.

Disease burden estimates are based on actual active surveillance. The estimated 1,000 deaths a year caused by polio reflect past infections and current deaths. Following Robertson (1993), we obtained the number of cases and deaths in the absence of immunization by applying an incidence rate of 1 per 1,000 population under age five and CFRs of from 2.5 percent in developed countries to 10.0 percent in Sub-Saharan Africa. To determine current cases, we applied an estimate of notification efficiency to reported cases.

Measles

Measles is an acute respiratory viral infection. Children born to immune mothers are protected against clinical measles from passively acquired maternal antibodies until they are five to nine months of age. More than 90 percent of infections are associated with clinical disease (Krugman 1963). Complications include pneumonia, diarrhea, encephalitis, and blindness, especially in children with vitamin A deficiency. In recent years, CFRs have been estimated at 3 percent in many developing countries, but historically they have been as high as 30 percent in some community-based studies (Aaby 1988; Aaby and Clements 1989; Moss, Clements, and Halsey 2003; Perry and Halsey 2004).

For a disease such as measles in which infection is almost universal in the absence of immunity, small changes in the CFR result in large changes in estimates of total mortality. Increased complication and mortality rates occur in children who are younger than five, vitamin A deficient, or infected with HIV or who have acquired measles from a household contact (Perry and Halsey 2004). Declines in CFRs in the past two decades are associated with the tendency of the disease to infect older children, decreased crowding, and improved nutritional status in many developing countries (Perry and Halsey 2004). At the same time, recent studies indicate CFRs of 0.4 to 9.7 percent in Sub-Saharan African countries with low immunization coverage (Perry forthcoming).

Considerable controversy is associated with the number of deaths resulting from measles, because of difficulty in accurately specifying the cause of death in children afflicted with measles and in separating complications of measles from those of other conditions. In addition, CFRs, which have decreased rapidly in many countries, vary significantly. The natural history model used in this chapter is based on Stein and others (2003), modified to account for the effect of supplementary immunization activities.

We derived estimates of the burden of disease in countries with high-quality surveillance data and high sustained coverage of measles vaccine by adjusting the number of reported cases by a reporting efficiency factor ranging from 5 to 40 percent. In estimating the future burden of disease, the averted burden of disease, and the burden in countries without both adequate surveillance and sustained high coverage, we assumed that the average number of cases per year is equal to the number of children in the current birth cohort who are not protected by either routine or supplemental vaccination. WHO (2005a) estimates that in 2001, 611,000 deaths (approximately 5 percent of all childhood mortality) were attributable to measles.

An alternative proportional mortality approach, which is based on retrospective verbal autopsy studies in 18 countries to derive the proportional causes of child deaths in 42 high-mortality countries, also has appeared in the literature (Morris, Black, and Tomaskovic 2003). This model suggests that measles may have accounted for approximately 3 percent of all childhood deaths in 2000.

In countries with a high disease burden, the true number of measles deaths may be somewhere between the proportional mortality and natural history estimates. WHO (2005b) uses a hybrid method that estimates that measles was responsible for an average of 4 percent of mortality among children under five between 2000 and 2003, or approximately 400,000 deaths per year. If the actual number of deaths in 2001 was 400,000, then the cost per death averted will be lower than what has been estimated for this chapter, and the effect of increasing coverage will be overestimated because fewer deaths could be prevented.

Both of the approaches described have strengths and limitations. We adopt the natural history approach for this analysis because the chapter includes deaths at all ages and the model can adapt to recent changes in CFRs and coverage rates.

However, the natural history method is sensitive to the accuracy of parameter inputs such as CFRs and may underestimate the effect of herd immunity. Further modeling efforts would need to incorporate sensitivity testing around a range of parameter estimates.

In the absence of vaccination, the measles virus would infect almost 100 percent of the population, including most of the 688 million children under five in the developing world. Using the methods described here, approximately 125 million cases and 1.8 million to 2.0 million deaths per year would be expected in the absence of vaccination.

Haemophilus influenzae Type b (Hib)

Hib is transmitted through the respiratory tract and causes meningitis, pneumonia, septic arthritis, skin infections, epiglottitis, osteomyelitis, and sepsis. Deaths caused by Hib occur primarily from meningitis and pneumonia. In developed countries, approximately half of diagnosed invasive infections are meningitis (Wenger and Ward 2004). In developing countries, a larger proportion of identified cases is meningitis resulting from underdiagnosis of other clinical syndromes (Martin and others 2004; Peltola 2000). Intervention studies have demonstrated significant reductions in pneumonia in vaccinated compared with unvaccinated children (Levine and others 1998; Mulholland and others 1997). Although infections occur throughout the world, the incidence of Hib disease may be lower in some Asian countries than in Africa and the Americas (Gessner and others 2005).

We derived estimates of Hib disease burden from incidence rates and CFRs for meningitis and pneumonia. We derived country-specific estimates of the incidence of Hib meningitis from the literature on incidence in the prevaccine era (Bennett and others 2002). For countries without meningitis incidence data, we used the average incidence in countries with similar epidemiological profiles. Regional averages ranged from 219 cases per 100,000 to 3 per 100,000 population in children under one, and 1 to 15 per 100,000 population in children age one to four. The CFR for meningitis is nearly 100 percent in the absence of intensive antibiotic therapy, but it can be reduced to 5 to 8 percent when appropriate therapy is available (Swartz 2004). We derived CFRs in a manner similar to that used for incidence rates and adjusted them on the basis of country-specific data on access to care. Regional means ranged from 3 to 32 percent.

Estimating the burden of Hib pneumonia is much more complex. A rapid assessment method assumes five pneumonia cases for every meningitis case (WHO 2001). An alternative approach assumes that Hib is responsible for a fixed proportion (about 20 percent) of acute lower respiratory infection deaths in the absence of immunization (Peltola 2000). We derived pneumonia CFRs from a literature review of lower respiratory infections in children (Bennett and others 2002), with average CFRs ranging from 1 percent among infants in developed countries to 12 percent in Sub-Saharan Africa.

Hepatitis B

In many developed countries, most transmission of hepatitis B occurs during or after adolescence, coinciding with the onset of sexual activity and of drug abuse involving unsafe reuse of needles and syringes (McQuillan and others 1999). In many African countries, transmission occurs primarily in early childhood through mucosal contact with infectious body fluids and unsafe injection practices (Margolis, Alter, and Hadler 1997). Some Asian countries have a high rate of chronic carrier states, and the primary mode of transmission is mothers to infants (Beasley 1988; Mast and others 2004). The rate of symptomatic disease is only about 1 percent in infancy and 10 percent in early childhood, but it increases to 30 to 40 percent in adults. Serosurveys for carrier states of hepatitis B are available for almost all nations (WHO 1996).

Models of hepatitis B disease burden are based on estimated ratios between infected and carriage states at various ages or estimates of the percentage of carriers that progress to hepatoma, fulminant hepatitis, or cirrhosis at later stages of life (Miller and McCann 2000). The model we used for estimating hepatitis B mortality estimates the age- and sex-specific progression of hepatitis B surface antigen infection to disease incorporating competing mortality, particularly because individuals infected with HIV are more likely to perish from HIV before the full mortality impact from hepatitis B infection (Gay and others 2001; Griffiths, Hutton, and Pascoal 2005).

Whereas most vaccine-preventable diseases that result in death occur at an early age shortly after the age of vaccination, deaths from hepatitis B occur many years into the future. Countries that introduce hepatitis B vaccines today will not reap most of the benefits for many years. In the absence of vaccination, we estimated approximately 1.4 million future deaths attributable to hepatitis B for the 2001 birth cohort after accounting for competing mortality. Global vaccination of 35 percent would prevent more than 500,000 of those future deaths. Discounting the value of future hepatitis B deaths to their equivalent value in the present to make the burden of disease prevented equivalent to that of other vaccine-preventable diseases results in approximately 87,000 deaths averted.

Yellow Fever

Yellow fever virus is transmitted by mosquitoes, primarily *Aedes eqypti,* with a three- to six-day incubation period. Patients present with intense headache, fever, chills, and myalgia, among other symptoms. Although once much more widespread, yellow fever is now limited to West and Central Africa, the northern half of South America, and Panama. In approximately

15 to 20 percent of yellow fever patients, severe disease occurs, with liver and kidney failure and cardiovascular collapse. The CFR varies, with increased severity in older adults (Monath 2004). The average CFR in patients in Africa with jaundice is 20 percent (Monath and others 1980; Nasidi and others 1989).

On the basis of surveillance data adjusted for underreporting, WHO (1992) estimates the global burden of yellow fever at 200,000 cases and 30,000 deaths in 1990. Most cases and deaths occur in 33 African countries, where 1 in 80 cases is assumed to be reported. In South American countries, 1 in 10 cases is assumed to be reported. We use the implied incidence rate and a CFR of 15 percent to project future mortality. Between 1990 and 2001, some improvement in routine coverage of yellow fever vaccine occurred, but the overall burden of yellow fever is unlikely to have declined.

ESTIMATES OF THE CURRENT BURDEN OF VACCINE-PREVENTABLE DISEASES AND OF THE BURDEN AVERTED BY VACCINATION

Table 20.2 provides WHO estimates of deaths from selected vaccine-preventable diseases for 2001, taking immunization coverage rates into account. The greatest burden of disease is in Sub-Saharan Africa, which accounts for 58 percent of pertussis deaths, 41 percent of tetanus deaths, 59 percent of measles deaths, and 80 percent of yellow fever deaths. East Asia and the Pacific has the greatest burden from hepatitis B, with 62 percent of deaths worldwide. South Asia also experienced a high disease burden, particularly for tetanus and measles.

Table 20.2 also shows the extent of mortality in the absence of immunization and the estimated number of deaths averted by vaccination. In 2001, vaccination averted up to 52 percent of yellow fever deaths, 61 percent of measles deaths, 69 percent of tetanus deaths, 78 percent of pertussis deaths, 94 percent of diphtheria deaths, and 98 percent of polio deaths that would have occurred in the absence of vaccination. These results demonstrate the significant effect that vaccination programs have had on worldwide disease burden. The figures also show that vaccination programs have been less successful in reducing the disease burden in Sub-Saharan Africa, where coverage rates are lower.

Table 20.3 reports WHO estimates of disability-adjusted life years (DALYs) lost from vaccine-preventable diseases by region for 2001, demonstrating the high burden of disease worldwide from disability associated with sequelae of hepatitis B (liver cancer and cirrhosis), pertussis, and tetanus.[2]

EXPANDED PROGRAM ON IMMUNIZATION

WHO initiated the EPI in 1974 to provide countries with guidance and support to improve vaccine delivery and to help make vaccines available for all children (Hadler and others 2004; Turk 1982; WHO 1974). A standard immunization schedule was established in 1984 on the basis of a review of immunological data for the original EPI vaccines: BCG, diphtheria-tetanus-pertussis (DTP), oral polio, and measles vaccines (Halsey and Galazka 1985).

Today, national immunization programs in developing countries are responsible for improving access to the traditional EPI antigens and introducing new vaccines. In 2002, the EPI introduced the Reaching Every District strategy, which focused on achieving an 80 percent coverage rate of DTP3 in 80 percent of districts and using immunization contacts to deliver other high-priority child health interventions. In addition to delivering vaccinations, national immunization programs are concerned with the quality and safety of immunization through the adoption of safe injection technologies (autodisabled syringes, storage boxes, and incinerators) and proper cold chain and vaccine stock maintenance.

In most developing countries, immunizations are provided through a system of fixed facilities at different levels of the health system. Immunization campaigns are discrete, time-limited efforts at national or subnational levels that usually focus on specific antigens (for example, polio). Mobile strategies rely on the use of specialized vehicles to transport health professionals and vaccines to deliver services to remote or migrating populations. Outreach is a strategy by which staff members from a health facility travel to villages and surrounding areas to administer vaccines. Extended outreach refers to more targeted and intensive efforts.

In 1999, the major international development partners involved in immunization (for example, WHO, UNICEF, the World Bank, and bilateral donors) joined the Bill & Melinda Gates and Rockefeller Foundations, the vaccine industry, and nongovernmental organizations to create GAVI (http://www.vaccinealliance.org) to increase access to new and underused vaccines in the world's poorest countries, improve access to basic immunization services, and accelerate research and development pertaining to new vaccines and delivery technology. Through the Vaccine Fund, GAVI raised more than US$1.3 billion to strengthen immunization systems, introduce new vaccines, and support safe injection practices. More than US$3 billion has been pledged for the next 10 years. Between 2000 and 2003, an additional 4 million children were vaccinated with DTP3, 42 million with hepatitis B, nearly 5 million with Hib, and more than 3 million with yellow fever vaccine.

COSTS AND COST-EFFECTIVENESS OF EXISTING VACCINATION PROGRAMS

Brenzel and Claquin (1994) and GAVI (2004) estimate the cost per fully immunized child (FIC) for the traditional six EPI antigens as approximately US$20.[3] We evaluated the cost per

Table 20.2 Estimated Number of Deaths in the Absence of Vaccination, Deaths from Vaccine-Preventable Diseases, and Deaths Averted by Vaccination, All Ages, by Region and Vaccine, 2001
(thousands)

Disease	Total	High income	East Asia and the Pacific	Europe and Central Asia	Latin America and the Caribbean	Middle East and North Africa	South Asia	Sub-Saharan Africa
Diphtheria								
If no vaccination	78	3	28	4	8	5	21	10
Estimated deaths	5	<1	1	<1	<1	<1	3	1
Deaths averted	73	3	27	4	8	5	18	9
Pertussis								
If no vaccination	1,343	7	377	4	138	93	428	296
Estimated deaths	301	<1	3	<1	6	8	108	176
Deaths averted	1,042	7	374	4	132	85	320	120
Tetanus								
If no vaccination	936	<1	110	<1	20	23	543	239
Estimated deaths	293	<1	27	<1	1	4	140	121
Deaths averted	643	<1	83	<1	19	19	403	118
Poliomyelitis								
If no vaccination	52	1	15	1	3	4	17	11
Estimated deaths[a]	<1	<1	<1	0	0	0	0	0
Deaths averted	51	n.a.	15	1	3	4	17	11
Measles								
If no vaccination	2,000	6	301	36	6	55	567	1,025
Estimated deaths[b]	676	<1	77	4	<1	7	239	348
Deaths averted	1,237	5	229	28	6	40	351	578
Hib								
If no vaccination	468	<1	28	2	9	14	199	216
Estimated deaths	463	<1	28	2	5	14	199	215
Deaths averted	5	<1	<1	<1	4	<1	<1	1
Hepatitis B								
If no vaccination	600	34	370	36	11	17	75	58
Estimated deaths	600	34	370	36	11	17	75	58
Deaths averted[c]	<1	<1	<1	<1	<1	<1	<1	<1
Yellow fever								
If no vaccination	63	n.a.	n.a.	n.a.	8	n.a.	n.a.	54
Estimated deaths	30	n.a.	n.a.	n.a.	6	n.a.	n.a.	24
Deaths averted	33	n.a.	n.a.	n.a.	2	n.a.	n.a.	30

Source: Mathers and others 2006 and authors' calculations.
n.a. = not available.
Note: Totals may not add due to rounding.
a. Primarily deaths at older ages caused by delayed effect of poliomyelitis in childhood.
b. See text for discussion of uncertainty regarding measles estimates. The values shown here are an updated version of the 2001 estimates.
c. Deaths averted to date from the use of the hepatitis B vaccine in infant immunization programs are minimal, largely because of the long time period (20 to 40 years) to see mortality effects.

Table 20.3 DALYs Lost from Vaccine-Preventable Diseases, All Ages By Region, 2001
(thousands)

Disease	Total	High income	East Asia and the Pacific	Europe and Central Asia	Latin America and the Caribbean	Middle East and North Africa	South Asia	Sub-Saharan Africa
Diphtheria	164	<1	18	2	8	1	90	45
Tetanus	8,342	5	762	2	17	110	3,965	3,481
Pertussis	11,542	139	584	81	366	326	3,930	6,116
Poliomyelitis	145	8	49	2	6	8	55	17
Measles	23,129	23	2,318	236	13	470	6,527	13,539
Hepatitis B[a]								
Acute hepatitis B	2,169	86	675	79	95	111	585	536
Liver cancer	9,168	1,223	5,925	379	277	138	464	762
Cirrhosis of the liver	15,780	2,146	3,890	2,084	1,513	686	4,249	1,212
Meningitis[b]	5,607	131	1,071	403	591	328	2,142	941
Lower respiratory infections[c]	85,920	2,314	10,827	2,111	3,043	2,974	34,196	30,455

Source: Mathers and others 2006 and Authors' calculations.
Note: Totals may not add due to rounding.
a. Includes all DALYs attributable to the three conditions. Hepatitis B is the underlying cause of only a portion of the liver cancer and cirrhosis of the liver DALYs.
b. Includes all DALYs attributable to meningitis, including Hib, *S. pneumococcus*, and *N. meningitides.*
c. Includes all DALYs attributable to lower respiratory infections, including Hib and *S. pneumococcus.*

FIC for the childhood EPI cluster antigens by World Bank region on the basis of published and unpublished data. These studies used a standard costing approach that estimated the costs of labor, vaccines, supplies, transportation, communication, training, maintenance, and overhead and included the annualized value of equipment, vehicles, and building space (Khaleghian 2001; USAID, Asia–Near East Region 1988; WHO 1988). The number of FICs in these studies was measured using community-based sample surveys (Henderson and Sundaresen 1982).

Our literature review found 102 estimates of total and unit immunization program costs from 27 countries between 1979 and 2003 for different immunization delivery strategies (Berman and others 1991;1 Beutels 1998, 2001; Brenzel 2005; Brenzel and Claquin 1994; Brinsmead, Hill, and Walker 2004; Creese 1986; Creese and Domínguez-Ugá 1987; Domínguez-Ugá 1988; Edmunds and others 2000; Griffiths and others 2004; Levin and others 2001; Pegurri, Fox-Rushby, and Walker 2005; Robertson and others 1992; Soucat and others 1997; Steinglass, Brenzel, and Percy 1993). All costs were converted to 2001 U.S. dollar equivalents. Because total and unit costs are related to population size, table 20.4 reports population-weighted results only. National immunization program refers to total national costs for all strategies.

The population-weighted mean cost per FIC for all regions and all strategies is approximately US$17, with a range of US$3 to US$31. The lowest mean population-weighted cost per FIC was for extended outreach services (US$5.81), perhaps because the strategy is a more targeted approach. Routine facility-based strategies had lower average costs (US$13.65 per FIC) than campaigns (US$26.82 per FIC) or mobile strategies (US$25.84 per FIC). Higher unit costs associated with these strategies are possibly attributable to a different mix of inputs as well as greater expenses for per diems, fuel, and social mobilization. The results also vary by World Bank region, with East Asia and the Pacific (US$13.25) and Sub-Saharan Africa (US$14.21) having lower estimates of cost per FIC than Europe and Central Asia (US$24.12) and the Middle East and North Africa (US$22.15).

The findings of our analysis are generally supported by the literature (Creese 1986; Brenzel and Claquin 1994; Khaleghian 2001), which has shown that variation in the cost per FIC is related to the mix of delivery strategies, the prices of key inputs such as vaccines, and the overall scale of programs. In addition, an analysis of 13 national financial sustainability plans for immunization reveals a wide range in the cost per FIC by region and strategy.[4]

Recurrent costs are the lion's share of total immunization costs (80 percent for fixed facility strategy and 92 percent for campaigns), which has implications for the need for continuous and predictable program financing. Labor costs account for the largest share (roughly 30 to 46 percent of total cost) for all strategies except extended outreach. Vaccine costs range from 8 percent for mobile strategies to 29 percent for extended

Table 20.4 Estimates of the Population-Weighted Annual Cost for the Traditional Vaccines per FIC, by Immunization Strategy and Region, 2001
(2001 US$)

Strategy	East Asia and the Pacific ($n = 4$)	Europe and Central Asia ($n = 1$)	Latin America and the Caribbean ($n = 1$)	Middle East and North Africa ($n = 1$)	South Asia ($n = 10$)	Sub-Saharan Africa ($n = 15$)	All regions ($n = 32$)
National immunization program	—	—	18.10	22.15	24.82 (23–27) $n = 2$	21.05 (17–26) $n = 2$	23.52 (17–27) $n = 6$
Fixed facility	20.00 (18–22) $n = 2$	24.12	—	—	13.79 (6–24) $n = 7$	6.31 (3–31) $n = 6$	13.65 (3–31) $n = 16$
Campaign	—	—	—	—	—	26.82 (13–28) $n = 3$	26.82 (13–28) $n = 3$
Mobile	—	—	—	—	—	25.84 $n = 1$	25.84 $n = 1$
Outreach	6.50 (4–9) $n = 2$	—	—	—	7.11 $n = 1$	—	7.10 (4–9) $n = 3$
Extended outreach	—	—	—	—	—	5.81 (5.8–13) $n = 3$	5.81 (5.8–13) $n = 3$
Mean for all strategies	13.25 (4–22)	24.12	18.10	22.15	17.11 (6–27)	14.21 (3–31)	16.91 (3–31)

Source: Authors' calculations for the traditional vaccines based on the literature.
— = not available.
Note: Mean values are used in the analysis. Ranges for estimates are reported in parentheses. Europe and Central Asia, Latin America and the Caribbean, and the Middle East and North Africa are limited to one observation for each region, which may not be indicative of the cost per FIC in each region. However, in lieu of using region-specific estimates, the overall average (US$13.65) would be applied, which may underestimate the cost per FIC in these more developed regions, where higher unit costs for delivery of health services would be expected.

outreach strategies. Transportation costs account for the second-largest share of EPI costs for mobile strategies, while building costs account for a greater share of fixed facility strategies.

Using data from table 20.4 on costs per FIC and multiplying by the size of the population covered, we estimate US$1.17 billion for the total cost of immunization programs in developing countries in 2001, with a range of US$717 million to US$1.48 billion. At US$20 per FIC, the cost of the six traditional vaccines in developing countries would have amounted to US$1.57 billion in 2001. Table 20.5 shows that the estimated cost per death averted ranges from US$205 in South Asia and Sub-Saharan Africa to US$3,540 in Europe and Central Asia. These results suggest that the cost per death averted rises with coverage rates. Europe and Central Asia, Latin America and the Caribbean, and the Middle East and North Africa had higher coverage rates in 2001, resulting in fewer deaths that could be averted. The table also shows that the cost per DALY from the traditional EPI vaccines ranges from US$7 to US$438, depending on region, mix of strategy, and levels of scale.

Our analysis highlights the variation in cost per FIC by region and strategy and demonstrates the value of more disaggregated results for making policy decisions. However, given the limited sample of estimates available for the regions and strategies, the results should be used as an indicative guide for policy making and not as a substitute for country-specific cost-effectiveness evaluations of strategies. In addition, our estimates do not take into account household costs, such as time spent seeking services, and other social costs. Our estimates also do not consider the direct and indirect costs of acute illnesses prevented by vaccination or the costs of long-term complications from disease and of adverse events associated with vaccination (though the latter are unlikely to have a significant impact on costs because rates of serious complications are extremely low). Furthermore, the analysis focuses on FICs and underemphasizes the benefits of partial immunization. Future economic evaluations of immunization program alternatives could consider these factors as a critical step in determining the allocation of scarce resources among high-priority health interventions.

Table 20.5 Average Cost per FIC, Total Immunization Cost, Cost per Death Averted and Cost per DALY for the Traditional Immunization Program by Region

Strategy	East Asia and the Pacific	Europe and Central Asia	Latin America and the Caribbean	Middle East and North Africa	South Asia	Sub-Saharan Africa
Cost/FIC (2001 US$) (from table 20.4)	13.25	24.12	18.10	22.15	17.11	14.21
Percentage of FIC	78.22	93.72	86.36	90.90	58.86	50.20
Estimated total immunization cost (2001 US$ millions)	316	131	174	152	227	172
Estimated deaths averted (thousands, from table 20.2)	728	37	174	153	1,109	867
Estimated cost/death averted (2001 US$)	434	3,540	1,030	993	205	205
Estimated cost/DALY (2001 US$)	85	395	438	166	16	7

Source: Authors' calculations.
Note: DALY estimates are the sum total for diphtheria, pertussis, tetanus, polio, and measles from table 20.3.

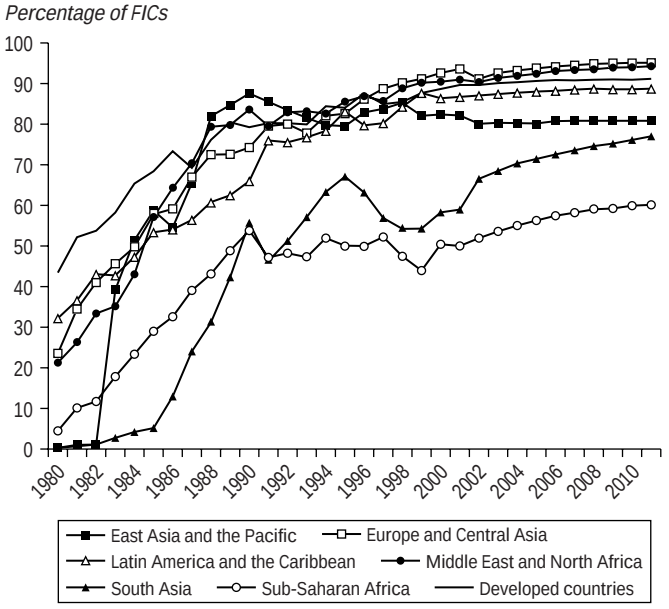
COST-EFFECTIVENESS OF INCREASING IMMUNIZATION COVERAGE FOR THE TRADITIONAL EPI

WHO (2004) estimates that in 2001, 30 million children were inadequately immunized with DTP. Achieving higher coverage rates by improving access for remote populations, accelerating immunization delivery strategies, and introducing new vaccines will mean increasing the level of investment (Batt, Fox-Rushby, and Castillo-Riquelme 2004).

We estimated the costs of scaling up EPI coverage for a hypothetical population of 1 million in each region between 2002 and 2011. Costs were reported in 2001 dollars, and a 3 percent discount rate was applied. Brenzel (2005) provides details on the methods. The costs of scaling up coverage are based on vaccine and delivery costs per dose. We derived vaccine costs from the unit price of each vaccine (provided by WHO, UNICEF, and the Vaccine Fund); wastage rates for vaccines and injection supplies by strategy; the required injection supplies; and the number of doses per FIC. A 2 percent adjustment was made for inflation. We used data on the cost per FIC generated earlier to derive delivery costs per dose by strategy and region by subtracting the costs of vaccines, injection supplies, and fixed costs.

Fixed costs were excluded from the scaling-up exercise because they were assumed to remain constant during the projection period.

- First, the largest projected coverage increase of 9 percentage points (figure 20.1) may not require additional infrastructure investments.
- Second, how and to what extent fixed costs would change by region is uncertain, and a conservative approach would be to exclude them.
- Third, because most immunization costs are recurrent costs, the analysis focuses on these.



Source: Authors' estimation.

Figure 20.1 Coverage of FICs Projected to 2011

- Finally, because the scale factor is derived from the unit costs of a health center visit, the assumption of constant fixed costs in the short run appears reasonable.

Previous studies have found that the main cost drivers of immunization costs are the mix of strategies and the scale of immunization programs (Brenzel and Claquin 1994; Domínguez-Ugá 1988; Robertson and others 1992; Soucat and others 1997). Countries are unlikely to achieve 90 percent or more coverage relying on fixed facilities alone because of limited population access. We estimate the proportion of FICs obtained for each strategy by region.[5] The best mix of strategies for increasing coverage will vary by country depending on the

dispersion of the population, the access to health facilities, the vaccines being delivered, and the effectiveness of various strategies in reaching target populations. Estimates are also adjusted for the level of scale by a factor derived from the unit cost per health center contact by coverage level (Mulligan and others 2003), and details are provided in Brenzel (2005).

The total additional cost of reaching higher coverage levels was divided by the number of deaths averted. Coverage projections for 2002–11 were based on statistical modeling of official WHO and UNICEF estimates for the period between 1995 and 2002 for all developing countries. The model relates coverage in future years to that in the previous year, with the relationship between past and future coverage differing for each region and economic status combination.

Figure 20.1 shows historical and projected coverage rates by region. The figure shows that coverage increased in all the regions during the late 1980s under universal childhood immunization. After 1990, when funding for universal childhood immunization waned, the figure indicates the subsequent stagnation and, in some cases, the declines in coverage rates. For the scaling-up period, we project that the coverage of FICs will increase from 78 to 79 percent in East Asia and the Pacific, from 92 to 95 percent in Europe and Central Asia, from 88 to 90 percent in Latin America and the Caribbean, from 91 to 95 percent in the Middle East and North Africa, from 70 to 79 percent in South Asia, and from 52 to 61 percent in Sub-Saharan Africa. The projections show that three of the six regions are expected to achieve 90 percent FIC by 2011. East Asia and the Pacific, South Asia, and Sub-Saharan Africa will require additional intensive efforts to achieve higher coverage rates.

Table 20.6 reports the results of the scaling-up analysis for the traditional EPI vaccines, for tetanus toxoid vaccination for women of reproductive age, and for selected new vaccines. The discounted incremental cost per child vaccinated with the traditional EPI vaccines ranges from US$10.89 in Latin America and the Caribbean to US$12.84 in the Middle East and North Africa. The number of discounted deaths averted because of full immunization depends on incremental coverage rates and varies from 747 in Europe and Central Asia to 14,584 in Sub-Saharan Africa, resulting in regional variations in the discounted incremental cost per death averted from US$169 in Sub-Saharan Africa to US$1,754 in Europe and Central Asia.[6]

DALYs were estimated indirectly based on the ratio of deaths to DALYs for each disease in 2001. This ratio is applied to the hypothetical population in each World Bank region over the projection period. Calculated this way, the number of DALYs averted will not account for changes in the average age of infection that ordinarily results from expanding immunization coverage. This method over-estimates the number of DALYs and thus under-estimates the cost/DALY. Cost-effectiveness ratios should be treated as indicative only. The cost/DALY ranges from $2 to $20 for scaling up traditional immunizations.

For tetanus toxoid immunization, the additional discounted cost per person vaccinated ranges from US$3.28 to US$4.06. The cost per death averted varies from US$271 to more than US$190,000. The results of this analysis fall within the range of estimates reported in the literature (Berman and others 1991; Steinglass, Brenzel, and Percy 1993). Differences in coverage levels and in protection against neonatal tetanus through skilled delivery contribute to the variation in results across regions.

The analysis shows both an increase in costs and potential benefits from scaling up immunization programs. In practice, the costs and benefits related to scaling up in any one region will be highly dependent on a few countries or subnational areas within countries. Aggregate country- or region-level data do not reveal the efficiency that could best be obtained by targeting immunization efforts on specific countries or geographic areas rather than making diffuse investments across regions. For instance, Miller and others (1998) show that India and Nigeria contribute the most to estimates of global measles deaths; therefore, reducing transmission in those countries would contribute the most to reducing the global disease burden caused by measles.

Despite its importance for policy, empirical and country-specific evidence on how immunization program costs change as coverage increases is lacking. Because scaling up immunization coverage will require more intensive efforts to find unvaccinated children, an extra cost for vaccinating each additional child is generally expected. Nevertheless, most cost-effectiveness studies assume constant returns to scale (Elbasha and Messonnier 2004; Karlsson and Johannesson 1998) even when emerging evidence suggests that the cost of vaccinating each additional child may rise with the size of delivery unit (Valdmanis, Walker, and Fox-Rushby 2003). Box 20.1, which focuses on scaling up traditional immunization coverage, and box 20.2, which focuses on new antigens, summarize the results of two studies that shed more light on this subject.

COSTS AND COST-EFFECTIVENESS OF ADDING NEW ANTIGENS TO THE CURRENT IMMUNIZATION SCHEDULE

We also estimated the additional costs per person vaccinated and cost per death averted of introducing new and underused vaccines into the traditional EPI in a hypothetical population of 1 million in each region between 2002 and 2011. The new vaccines considered protect against hepatitis B, yellow fever, Hib, measles, rubella, Japanese encephalitis, and meningococcal A, as well as inactivated polio vaccine (IPV). For comparison purposes, we assumed that new vaccines were introduced in 2002.

The additional cost of combination vaccines is net of the original cost of DTP vaccination to avoid duplication. The

Table 20.6 Average Cost per Person Vaccinated and per Death Averted for Scaling Up Immunization Coverage and Adding in Selected New Vaccines in a Hypothetical Population of 1 million for 2002–11
(2001 US$, current vaccine prices)

	East Asia and the Pacific	Europe and Central Asia	Latin America and the Caribbean	Middle East and North Africa	South Asia	Sub-Saharan Africa
Traditional EPI (mix of strategies)						
Incremental discounted cost/person vaccinated	12.03	11.54	10.89	12.84	11.58	11.16
Incremental discounted deaths averted	3,165	747	2,552	4,576	7,584	14,584
Incremental discounted cost/death averted	478	1,754	791	698	274	169
Tetanus toxoid (mix of strategies)						
Incremental discounted cost/person vaccinated	4.06	3.34	3.28	3.34	3.98	3.88
Incremental discounted deaths averted	343	2	200	465	2,815	2,412
Incremental discounted cost/death averted	1,541	>190,000	3,117	1,880	271	394
Second opportunity for measles (fixed facility)						
Incremental discounted cost/person vaccinated	1.08	1.05	0.98	1.19	1.04	1.00
Incremental discounted deaths averted	1,138	599	95	1,304	2,509	9,646
Incremental discounted cost/death averted	119	199	1,906	228	74	23
Pentavalent vaccine DTP-HepB Hib (mix of strategies)						
Incremental discounted cost/person vaccinated	15.14	14.61	15.69	16.23	15.24	11.68
Incremental discounted deaths averted	139	39	129	318	248	1,952
Incremental discounted cost/death averted	13,697	42,529	22,540	12,564	10,950	1,319
Yellow fever (campaigns)						
Incremental discounted cost/person vaccinated	n.a.	n.a.	1.43	n.a.	n.a.	1.42
Incremental discounted deaths averted	n.a.	n.a.	94	n.a.	n.a.	376
Incremental discounted cost/death averted	n.a.	n.a.	2,810	n.a.	n.a.	834
Incremental discounted cost/person vaccinated (mix of strategies)						
Hepatitis B monovalent (birth dose)	2.26	2.15	2.36	2.37	2.24	2.02
DTP-hepatitis B (tetravalent)	7.85	7.57	7.34	8.03	7.55	7.26
Rubella (campaigns)	1.20	1.19	1.20	1.07	1.19	1.19
Meningococcal A (fixed facilities)	n.a.	n.a.	n.a.	2.73	n.a.	2.33
Japanese encephalitis (fixed facilities)	4.56	n.a.	n.a.	n.a.	4.37	n.a.
Injectable polio vaccine (monovalent)	7.12	6.72	6.42	7.32	6.85	6.60
Injectable polio vaccine (combination with DTP)	13.88	14.84	14.62	15.28	14.77	14.19

Source: Authors' calculations.
Note: n.a. refers to not applicable when a specific disease is not prevalent in a specific region.

delivery cost per FIC was apportioned to individual antigens on the basis of the share of number of doses per FIC for that antigen (Brenzel 2005). Cost estimates are based on the number of doses required for full immunity (that is, hepatitis B, Hib, and IPV vaccines require three doses for full immunity, and meningococcal A requires two doses for full immunity). Results are reported in table 20.6.

The analysis also assumes that an additional visit to a health facility is required for new doses (depending on timing in the EPI schedule). Combination vaccines may be more cost-efficient because of potential savings in supplies, syringes, and health workers' time, in addition to the overall health benefits of reducing the number of required injections. However, if the combination vaccine does not reduce the number of visits a child would ordinarily need to make to a health facility, any cost savings may be subsumed by the higher costs of increasing coverage.

The discounted incremental cost per person ranges from less than US$1 to US$16.23, depending on the unit price of

Box 20.1

Marginal Costs of Immunization Services in India

A study in Tamil Nadu evaluated immunization costs and coverage using a longitudinal panel dataset of immunization program costs (Brenzel 1995). Data were collected from a stratified, random sample of facilities between 1989 and 1991 for the North Arcot District Polio Control Program.[a] The sample included 120 observations of 59 different health centers: 17 followed for three years (29 percent), 27 followed for two years (46 percent), and 15 with a single observation (25 percent). Total immunization costs included the cost of labor, vaccines, injection supplies, transportation, and overhead and the value of equipment, vehicles, and buildings.

During this period, coverage rates for FICs increased from 5 to 77 percent. The table shows that the cost per dose and the cost per FIC increased during this period.[b] Changes in the cost per dose were highly statistically significant, whereas no statistical differences were apparent in the cost per FIC during the study period.

Comparison of Total Facility Immunization Costs, Immunization Activity, and Unit Costs by Year, North Arcot District Polio Control Program, 1989–91
(2001 US$)

Indicator	Year 1	Year 2	Year 3	Overall
Total costs	996	1,337	980	1,104
Variable costs	697	1,260	917	958
Cost/dose	1.09	1.98	1.33	1.47
Cost/FIC	13.11	27.92	17.07	19.37

Source: Brenzel (1995).

a. The program was a joint effort by the Indian Council for Medical Research, the Centre for Advanced Research in Virology at the Christian Medical Centre and Hospital in Vellore, and the governments of Tamil Nadu and India.

b. Higher costs in the second year reflect a change in the organization of the primary health care system in 1990 to improve access to basic services.

The study used data from the health facility sample to explain the determinants of immunization costs, which were modeled as a function of outputs, input prices, and other production-related variables that influence the cost function with respect to outputs. A random effects estimation was performed on the analysis sample relating the natural logarithm of health facility costs to the type of polio vaccine in use, estimated target population, and size of geographical area serviced by the health facility and natural logarithms of the number of FICs per facility, the number of hours spent by a village health nurse on immunization services per facility, and the number of small pieces of equipment used for immunization service delivery.

The analysis revealed a significant association between facility cost and the number of FICs, the hours worked by village health nurses, the area served, and the type of polio vaccine. When calculated using mean values, the marginal cost per FIC was Rs 24.43 (US$1.30) lower than the associated average cost per FIC of Rs 183 (US$9.80), implying that the average cost curve lies above the marginal cost curve for the sample of health facilities in India. A declining relationship is apparent between costs and coverage for this sample of facilities, calling into question assumptions of constant returns to scale. The results suggest that, in India, average cost-effectiveness ratios would overestimate total resource needs. Using a single-point estimate of average unit costs to determine the use of scarce public health resources will result in suboptimal resource allocations.

vaccine, the type of vaccine, the delivery strategy, and the coverage levels. The results lead to several conclusions:

- First, the additional incremental cost per person vaccinated is relatively small for some new vaccines.
- Second, because fixed costs are excluded, the results represent conservative estimates of additional costs.
- Third, because of price uncertainty, cost variations are greatest for newer vaccines, such as the DTP-IPV combination.

The second opportunity for measles has the lowest cost per death averted, ranging from US$23 to US$1,906 for fixed facility strategies, and from US$65 to US$1,363 for campaigns These results are consistent with the literature. Foster, McFarland, and John (1993) find an incremental cost per death averted ranging from US$335 to US$552 in urban areas and from US$327 to US$706 in rural areas. The Africa Measles Partnership (2004) estimates a cost per death averted of US$131 to US$393 in the African context, but these figures include the costs of infrastructure.

In the hypothetical populations, the incremental cost per death averted for the pentavalent vaccine ranged from US$1,319 in Sub-Saharan Africa to more than US$42,500 in Europe and Central Asia, depending mostly on the number of

Box 20.2

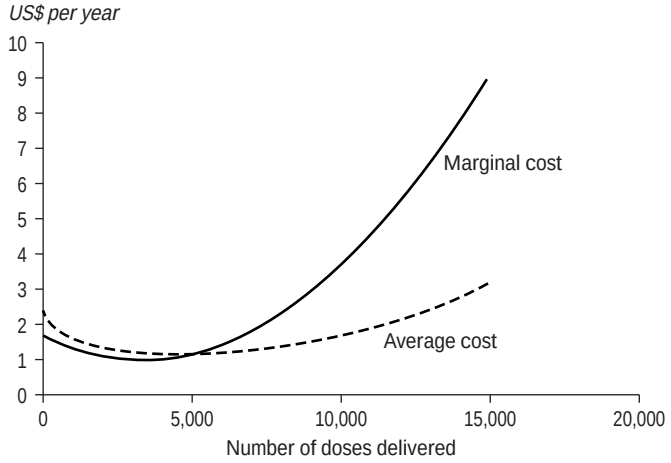
An Immunization Costing Study of Adding New Vaccines to the EPI in Peru

Data were collected from 19 government health facilities in three districts in Peru, including five hospitals and 14 health centers (Walker and others 2004). Total annual costs per center included vaccines, supplies, personnel, cold chain, overhead, and shared inputs. The average cost per dose for traditional EPI antigens plus yellow fever varied from US$1.50 to US$3.20 per dose as shown in the table, with vaccines and personnel accounting for the bulk of costs.

At 2,000 doses, the marginal cost of delivering one more dose is US$1.08, increasing to US$5.33 for 12,000 doses. Average and marginal costs are equal (US$1.18) when 5,000 doses are provided per site. When an outlier delivering many vaccines at a high cost was removed, cost-minimizing output rose to 6,000 doses at US$1.11.

Although each vaccination facility is likely to be associated with different average and marginal costs, considering vaccine provision across a range of providers is relevant, because targets for vaccination can be set by site. Information about marginal costs can help determine what the most efficient size for vaccination facilities is in the long run and how to minimize costs across different size units in the short run, given targets (see figure).

When hepatitis B, Hib, and the pentavalent vaccine (DTP-hepatitis B-Hib) are added to the delivery schedule, the total annual additional cost increases to US$4,121, US$11,886, and US$25,261, respectively, with an average incremental cost per dose of vaccine of US$0.20, US$4.14, and US$4.24, respectively. Adding these new vaccines increased the total cost of providing 5,100 doses from US$5,840 to US$9,415 and changed the minimum average cost from US$1.18 per dose to US$1.68. Therefore, the addition of new vaccines shifts both average and marginal costs upward.



Source: Authors' calculations.

Marginal and Average Vaccination in Sample Facilities in Peru *(2001 US$)*

Mean Cost per Dose by Type of Facility, Selected Districts in Peru *(2001 US$)*

Cost items	Health post	Health center	Rural hospital	Provincial hospital	Department hospital (Ayacucho)	National hospital
Recurrent items						
Vaccines	0.59	0.87	1.39	1.03	0.60	0.31
Syringes	0.04	0.05	0.07	0.04	0.05	0.03
Personnel	0.46	0.28	1.17	0.33	0.76	0.29
Other	0.05	0.03	0.03	0.04	0.03	0.13
Capital items	0.01	0.02	0.09	0.01	0.03	0.02
Direct costs	1.15	1.25	2.75	1.45	1.47	0.78
Indirect costs	0.33	0.26	0.41	0.30	0.45	1.19
Average cost	1.48	1.51	3.17	1.79	1.92	1.98

Source: Walker and others (2004).
Note: Totals may not sum exactly because of rounding.

potential deaths that could be averted. Although a wide range of results was found, these estimates are supported by the literature. Miller (1998) estimated between US$3,127 and US$3.2 million per life saved for Hib vaccine. Brinsmead, Hill, and Walker's (2004) systematic review of the literature on the cost-effectiveness of Hib vaccine finds wide variations in results because of methodological differences and epidemiological and health system characteristics. The discounted incremental cost of introducing the pentavalent (DTP–hepatitis B–Hib) vaccine is roughly equal to the total mean cost of the traditional vaccine package estimated earlier. This finding implies that introducing this combination vaccine may double the financial requirements, an implication that is supported by data from national financial sustainability plans for immunization (Lydon 2004).

The incremental discounted cost per person vaccinated with a birth dose of hepatitis B is approximately US$2, and that for the tetravalent vaccine was between US$7 and US$8. The 10-year time period for our analysis is too short to accumulate deaths averted resulting from hepatitis B vaccination because deaths from liver cancer occur at older ages. Beutels's (1998, 2001) reviews of studies of the cost-effectiveness of introducing hepatitis B vaccine indicate that results vary depending on assumptions of endemicity and the methodology used, with a cost per death averted ranging from US$3,500 to US$271,800.

Rubella vaccination had a low additional cost per person vaccinated, at slightly more than US$1. Golden and Shapiro (1984) found that vaccinating all prepubertal children with rubella vaccine had the highest benefit-cost ratio (ranging from US$1.70 to US$1.96). Most benefits were future cost savings from long-term institutional care. When rubella was delivered in combination with measles and mumps, the benefit-cost ratios varied from US$4.70 to US$38.80 (Hinman and others 2002).

The additional cost per person vaccinated with one dose of Japanese encephalitis vaccine was between US$4.37 and US$4.56. A study in Thailand using two doses showed a cost per child ranging from US$2.31 to US$4.20, depending on the mode of delivery (Siraprapasiri, Sawaddiwudhipong, and Rojanasuphot 1997). Ding and others (2003) estimate a cost per case averted of US$258 and a cost per DALY averted of US$16.80 for a five-dose inactivated Japanese encephalitis vaccine.

Our analysis suggests an additional discounted cost per person vaccinated for injectable polio vaccine of between US$6.60 and US$7.32, depending on coverage levels and mix of delivery strategy. The additional discounted unit cost of the combination DTP-IPV vaccine was higher, ranging from US$13.88 to US$15.28. These results are also sensitive to the current prices of the vaccine, which will probably decline in coming years. Brenzel (1995) finds that in India the cost per case prevented for the combination DTP-polio vaccine was much lower than for oral polio vaccine (OPV), primarily because the combination vaccine was associated with a greater reduction in the number of polio cases. Miller and others (1996) suggest that introducing IPV into routine vaccination in the United States would cost an additional US$15 million to US$28 million depending on the type of schedule adopted, resulting in a cost per vaccine-associated paralytic poliomyelitis case prevented of approximately US$3 million. Sangrugee, Caceres, and Cochi (2004) found that the least costly option would be for programs to stop providing OPV after postpolio eradication and certification and that optionally introducing IPV with universal IPV had the highest costs and the lowest expected number of vaccine-associated paralytic poliomyelitis cases. If the unit price of IPV fell to US$0.47, switching to IPV from OPV would be economically worthwhile.

FINANCIAL SUSTAINABILITY OF IMMUNIZATION PROGRAMS

Even though research has demonstrated that vaccination against childhood diseases is one of the most cost-effective health interventions, governments in many developing countries are considering how to meet the financing requirements of immunization programs, particularly as new vaccines are introduced and programs are scaled up. GAVI is working with countries to prepare for the transition from grant funding and to secure the overall financial sustainability of national programs. Approximately 55 countries have prepared national financial sustainability plans for immunization. These plans help countries evaluate the current and future costs and financing of national immunization programs and identify strategies to address future funding gaps (GAVI 2004; http://www.who.int/immunization_financing/en).

According to a recent analysis of financial sustainability plans, specific costs for immunization programs represent an average of 2 percent of total health spending and 6 percent of government health spending and are equivalent to less than 0.2 percent of gross domestic product on average. However, this profile changes after new and more expensive vaccines are introduced. In some countries, program-specific costs for immunization can reach as high as 20 percent of government health spending with introduction of combination vaccines (Lydon 2004). This share is related to the current unit price of the vaccine, which is expected to decline.

Governments and their development partners are challenged to find ways to finance and sustain immunization programs. In countries that are implementing reforms to achieve greater transparency and fiscal discipline through sectorwide approaches and medium-term expenditure frameworks, the additional financing requirements are compounded by the need to operate within a fixed budget for the health sector, so that increased funding needs for one program may necessitate budget cuts for others. This example illustrates the potential tradeoffs that exist at the country level, which create

both opportunities for more open policy dialogue in relation to priority setting for the use of scarce public funds and risks that the cost of new vaccines may not be readily integrated into national plans and budgets. Because of the financial implications of reaching higher coverage levels and simultaneously introducing new vaccines, policy makers will not only have to weigh the cost-worthiness of alternative investments but also have to understand their long-term budgetary implications.

IMPROVING THE COSTS AND COST-EFFECTIVENESS OF IMMUNIZATION PROGRAMS

The cost-effectiveness of immunization programs could be improved by either reducing costs or improving programs' health benefits. Programs could reduce costs by using a more efficient mix of delivery strategies, reducing vaccine wastage, and using lower-cost inputs while maintaining the same quality of service. Reductions in the price of vaccines in the near future will also reduce costs. Innovations in vaccine technology may result in more widespread use of vaccine vial monitors, and increased use of heat-stable vaccines could potentially reduce the cost of the cold chain, although these innovations may themselves add to costs. The number of children and adults immunized can be increased by creating additional demand for vaccination; reducing missed opportunities; and reducing the dropout rate between the first and third doses of DTP, hepatitis B, and other vaccines. Finally, changes in the EPI schedule could affect total costs by reducing the number of doses required to achieve immunity and thereby reducing the number of visits, resulting in savings in the costs of labor, supplies, transport, and perhaps overhead.

The EPI schedule was established in 1984 based on a review of immune responses to diphtheria, tetanus, pertussis, polio, and measles vaccines starting at different ages and with varying intervals between doses (Halsey and Galazka 1985). The EPI schedule administers three doses of DTP at the shortest possible intervals to complete the immunization series as early in life as possible. However, if the primary series could be reduced to two doses with a booster dose at 12 to 15 months of age, the cost savings from reduced visits and one fewer dose of DTP in countries that administer a fourth dose of DTP would be considerable. Additional serological studies would be needed to compare the existing EPI schedule with the theoretical schedule before a new schedule could be adopted. Also, other vaccines to be introduced into immunization programs would need to be revaluated in this schedule. Two doses of IPV administered beginning at two months of age induce protective levels of antibodies between 95 and 100 percent for each of the three polio types (Halsey and others 1997; Plotkin and Vidor 2004).

Some countries with a low incidence of tuberculosis (such as those of Eastern Europe) are considering the discontinuation of routine BCG vaccination, given the low risk of acquiring tuberculosis in early childhood. If the BCG were not administered during the first month of life, program costs would be reduced by the value of one visit and by the costs associated with vaccine purchase, shipping, storage, and administration.

RESEARCH AGENDA

Private and public sector investment in research and development pertaining to new vaccines and improved use of existing vaccines is considerable. Most research and development is focusing on vaccines likely to have the greatest effect in the developed world and the best financial return; however, by means of public-private partnerships for product development, foundations have stepped in to support vaccine research and development for diseases for which the greatest burden occurs in developing countries.

New vaccines are being developed that could be incorporated into EPI schedules, including vaccines that protect against rotavirus, *S. pneumoniae,* malaria, cervical cancer associated with human papilloma virus, HIV/AIDS, and dengue. New and improved vaccines are also being developed to protect against meningococcal infections in infancy and Japanese encephalitis (NIH 2000). WHO recently created the Initiative for Vaccine Research Department to facilitate global coordination of research and development efforts for these and other vaccines.

In compiling data for this chapter, we noted a number of key gaps in knowledge that could usefully drive a research agenda and contribute to more evidence-based policy making in the future (Fox-Rushby and others 2004). First, little is currently known about how and why delivery costs change with increasing numbers of vaccinations and at higher coverage rates and whether economies of scale can be achieved. Little is known about the relative cost-effectiveness of different strategies to increase coverage given different baseline coverage rates. This issue relates to other questions of the optimal timing for introducing new vaccines and of how decisions should vary given different epidemiological and economic settings. Future research should therefore consider the extent to which cost-effectiveness analyses need to be repeated for every country or context or whether (and how) estimating and validating relationships across countries and accounting for uncertainty in estimates of costs and effects are possible.

Second, more attention needs to be given to measuring effect. For example, even though the coverage of single antigens required to reach particular levels of FICs should be accounted for, economic evaluations need to move beyond such indicators of output to measuring effect on the quantity and qual-

ity of life. In evaluating different schedules, methodological research needs to focus on how to incorporate the combined effects of multiple vaccinations in this respect. Remarkably few studies have considered the effect on nonhealth benefits, such as economic growth and welfare. The larger the package of vaccinations considered, the more important this question becomes.

CONCLUSIONS

This chapter confirms that vaccination of children and women with the traditional EPI vaccines is a highly cost-effective public health intervention, although cost-effectiveness ratios vary by region, delivery strategy, and level of scale. Overall, vaccination has had a significant effect on reducing mortality and morbidity from childhood diseases and will be a priority intervention for achieving the child health Millennium Development Goals. Improving and sustaining measles control are among the most cost-effective interventions in high-mortality regions.

Establishing and maintaining high immunization coverage rates in many of the poorest developing countries have proven challenging for those with high population growth rates, limited infrastructure and resources, and fluctuating demand for services. According to historical coverage rate trends, Europe and Central Asia, Latin America and the Caribbean, and the Middle East and North Africa are expected to achieve 90 percent coverage of FIC by 2011, with East Asia and the Pacific, South Asia, and Sub-Saharan Africa lagging behind.

Increasing and sustaining higher immunization coverage rates will require further efforts so that disease control can be maintained, particularly when a perception exists at the community level that vaccine-preventable diseases are no longer a major public health issue. At higher coverage rates, further disease burden reductions will be smaller, which will affect relative cost-effectiveness. Targeted approaches in countries or at subnational levels could potentially yield high returns, especially in those areas with poor control of vaccine-preventable diseases.

Our analysis shows that the cost per FIC will increase as countries scale up immunization coverage and introduce new vaccines. Adding more antigens to traditional EPIs has been successfully accomplished in many countries, especially for Hib and hepatitis B vaccines. Although many of the new vaccines under consideration are more expensive than those for the original six targeted EPI diseases, they may still be relatively cost-effective compared with other interventions and with treatment costs. Our analysis shows a wide range of cost-effectiveness estimates depending on the type of vaccine, vaccine prices, coverage levels, and delivery strategy, with the additional incremental cost per person being relatively small for some new vaccines. Declines in unit prices of new vaccines also will affect cost-effectiveness results.

Financing and sustaining immunization programs are challenges that governments in developing countries and their development partners will face. The financial implications of reaching higher coverage levels and the simultaneous desire to introduce new vaccines will require policy makers to consider both the relative cost-effectiveness of interventions and the long-term budgetary implications.

Although global and regional estimates of cost-effectiveness of interventions are useful guides, further analytical work will be needed to evaluate the relative benefits (deaths and cases averted and DALYs) and costs (delivery and treatment) of vaccines for different delivery strategies and higher coverage rates, particularly at the country level.

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NOTES

1. For our analysis, the preimmunization era neonatal tetanus mortality rate per 1,000 live births is used: developed countries, 0.1; East Asia and the Pacific, 4.7; Europe and Central Asia, 0.4; Latin America and the Caribbean, 4.4; Middle East and North Africa, 4.7; South Asia, 15.3; and Sub-Saharan Africa, 10.2.

2. Because disease classification does not have a one-to-one correspondence with those prevented by vaccine, according to table 20.3 is based on estimates of the proportion of these illnesses that may be preventable by specific vaccines. For example, some meningitis and acute lower respiratory infections are caused by Hib or *S. pneumoniae,* and some cirrhosis is caused by hepatitis B.

3. A *fully immunized child* is a standard term that refers to a child who has received one dose of BCG vaccine, three doses each of oral polio vaccine and DTP vaccines, and one dose of measles vaccine. The number of FICs does not include children who have been partially immunized, so this measure underestimates the total effect on the disease burden. However, the number of FICs is representative of the effectiveness of the delivery system in providing access to immunization services to children. The authors are aware that fully vaccinating a child does not correspond to full immunity.

4. The mean population-weighted cost per FIC for the financial sustainability plans for immunization was US$21.06. The plans use DTP3 coverage as a proxy for FICs rather than coverage measured through population-based surveys (http://www.who.int/immunization_financing/en).

5. Assumptions about the relative distribution of FICs by strategy and region were based loosely on such factors as the proportion of the population with access to health services for fixed facilities and the likelihood of active mobile strategies.

6. A proxy for the total number of deaths averted is the sum of the individual deaths averted for each antigen in the traditional EPI. This figure may overestimate the actual number of deaths averted by fully immunizing children and therefore underestimate the cost per death averted.

However, the values estimated by region appear to support previously reported estimates, and direct estimation of deaths averted was impossible given data and model limitations.

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