Chapter 10

Vaccines for Children in Low- and Middle-Income Countries

Daniel R. Feikin, Brendan Flannery, Mary J. Hamel, Meghan Stack, and Peter M. Hansen

INTRODUCTION

Vaccination is the centerpiece of preventive care of the well child. Vaccination has been one of the singular public health successes of the past half century, and its full potential remains unrealized. Pneumonia and diarrhea, two of the leading causes of child mortality, account for approximately 1.4 million deaths annually (Liu and others 2016); vaccination with currently available vaccines has the potential to prevent 59 percent of pneumonia-related deaths and 29 percent of diarrhea-related deaths (Fischer Walker, Munos, and Black 2013). Other leading causes of childhood deaths are already preventable through available and effective vaccines, such as measles and meningitis, and other diseases, such as malaria, may become vaccine preventable in the near future (Agnandji and others 2011; Liu and others 2012). Forecasts for vaccine use in the 73 countries supported by Gavi, the Vaccine Alliance, project that 17.7 million deaths will be averted in children under age five years as a result of vaccinations administered from 2011 to 2020 (Lee and others 2013). Childhood vaccination contributed greatly to progress made toward achieving the fourth United Nations Millennium Development Goal, a two-thirds reduction in childhood mortality between 1990 and 2015 (UN 2015), and the centerpiece of several other major global initiatives (PHR 2014; WHO 2012a). Vaccination is central to the health goal included in the post-2015 Sustainable Development Goals, which is on a critical pathway to delivering on its targets.

In addition to the clear health benefits, vaccination has been one of the most cost-effective public health interventions (Brenzel and others 2006; WHO, UNICEF, and World Bank 2002). Based on 2001 data, the cost per death averted through routine vaccination with the six original antigens in the Expanded Program on Immunization (EPI) was US$205 in South Asia and Sub-Saharan Africa; estimated cost per disability-adjusted life year (DALY) averted was US$7 to US$16 (Brenzel and others 2006). New vaccines, although more expensive, have also been determined to be cost-effective in Gavi-eligible countries (Atherly and others 2012; Sinha and others 2007) (see box 10.1).

This chapter describes the epidemiology and burden of vaccine-preventable diseases and provides estimates of the value of vaccines in health impact as well as broader economic benefits. The focus is on vaccination of infants during routine well-child visits and not on other important vaccines for older children and young adults, such as human papillomavirus vaccine, typhoid vaccine, and dengue vaccines.

Corresponding author: Daniel R. Feikin, Chief, Epidemiology Branch/Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, United States; drf0@cdc.gov.

Box 10.1

Gavi, The Vaccine Alliance

Disparities exist in vaccination status between countries and within the same country, where some regions or sectors of society remain substantially undervaccinated. For example, in Nigeria's 2008 Demographic and Health Survey, the coverage of the third dose of the diphtheria-tetanus-pertussis vaccine varied from 67 percent in the southeast to 9 percent in the northwest (NPC and ICF Macro 2009). Disparities are largely driven by socioeconomic status; the poorest children, with the highest disease burden, are the least vaccinated (Cutts, Izurieta, and Rhoda 2013).

To address low coverage and inequitable access to life-saving vaccines, Gavi, the Vaccine Alliance was launched in 2000 to increase access to immunization in poor countries. Gavi is a public-private partnership involving the World Health Organization (WHO), the United Nations Children's Fund, and the World Bank; civil society organizations; public health institutes; donors and implementing country governments; major private philanthropists, such as the Bill & Melinda Gates Foundation; vaccine manufacturers; and the financial community (Gavi 2013). Gavi's support for 2011–15 has focused on 73 countries based on eligibility criteria determined through per capita gross national income.

Gavi has expanded its initial support for hepatitis B, pentavalent, and yellow fever vaccines to include measles vaccine second dose and those against pneumococcus, rotavirus, meningococcus serogroup A, measles-rubella, human papillomavirus, Japanese encephalitis, and inactivated polio vaccine. Gavi has approved a contribution to the global cholera stockpile for use in epidemic and endemic settings. From its inception through 2014, Gavi has committed US$8.8 billion in program support to eligible countries; 75 percent of the total commitment is for the purchase of vaccines. From 2000 through early 2015, Gavi-supported vaccines have helped countries vaccinate approximately 500 million children through routine programs. Annex table 10A.3 shows the vaccine introduction status in 73 Gavi-eligible countries.

Advanced Market Commitment

An innovative financing mechanism called the Advanced Market Commitment was established to accelerate the introduction of and scale up the pneumococcal conjugate vaccine through Gavi (Cernuschi and others 2011). The Advanced Market Commitment secured US$1.5 billion from six donor countries and the Bill & Melinda Gates Foundation, which provided a financial commitment to purchase pneumococcal conjugate vaccine for introduction and scale-up in Gavi-supported countries at predetermined terms.

Eligibility and Transition to Self-Financing

As of January 2014, per capita gross national income in 17 of 73 Gavi-supported countries had risen above the eligibility threshold, resulting in a five-year transition period during which such countries finance an increasingly larger share of their vaccines each year. These countries need to mobilize domestic resources to sustainably finance their vaccines when they complete the transition to self-financing.

Vaccine Investment Strategy

Gavi uses a vaccine investment strategy to determine which vaccines to add to its portfolio of support to countries every five years, taking into account the selection criteria and the date when different vaccines will be available. The Gavi Board decided in 2014 that Gavi will undertake the following:

- *Yellow fever*. Increase support for additional yellow fever campaigns.
- *Cholera.* Contribute to a global vaccine stockpile from 2014 to 2018 to increase access in outbreak situations and further a learning agenda on its use in endemic settings.
- *Malaria.* Consider supporting the vaccine that is now in development when it is licensed, WHO-prequalified, and recommended for use by the joint meeting of the WHO Strategic Advisory Group of Experts on Immunization and the Malaria Policy Advisory Committee.

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Box 10.1 (continued)

- *Rabies and influenza*. Recommend further assessment of the impact and operational feasibility of supporting rabies and influenza vaccines for pregnant women, fund an observational study to address critical knowledge gaps around access to rabies vaccine, and monitor the evolving evidence base for maternal influenza vaccination.

By forecasting and pooling demand from eligible countries and purchasing large volumes of vaccines, Gavi has created a reliable market for vaccines in these settings. Gavi's market-shaping strategy aims to ensure adequate supply to meet demand, minimize the cost of vaccines, and ensure the availability of quality and innovative products.

Improved vaccine delivery strategies are needed to ensure that immunization programs and health systems are able to implement programs of increasing size and complexity at high levels of coverage and equity. It will be necessary to build on the unprecedented momentum achieved in new vaccine introduction and market shaping to take to scale innovative approaches to generating demand for immunization; upgrading country supply chain management systems; strengthening country health information systems; and enhancing political will and country capacity related to leadership, management, and coordination.

METHODS

We describe vaccines in three categories:

- Vaccines among the six original EPI antigens: Bacille Calmette-Guérin (BCG); diphtheria, tetanus, and pertussis (DTP); and measles and polio
- Vaccines classified as new or underutilized and supported by Gavi since its inception in 2000
- New vaccines that might be introduced into routine immunization for infants at the well-child visit in the next decade.

For the epidemiology and vaccine characteristics, we used a nonsystematic review of the published literature, recommendations of the World Health Organization (WHO), and a search of relevant updated websites on vaccines. For the impact of vaccination using the original EPI vaccines, we referenced existing models. For the new vaccines, we used a methodology adopted through an expert process, with leading modeling groups co-convened by Gavi and the Bill & Melinda Gates Foundation, to estimate the number of future deaths and DALYs averted attributable to vaccinations administered in the 73 Gavi-supported countries (annex 10A and table 10A.1).

EXPANDED PROGRAM ON IMMUNIZATIONS

The EPI program was created in 1974 to improve vaccine availability globally (WHO 1974). Global policies and recommended schedules based on immunologic data were codified in 1984, with the goal of reaching every child with vaccines against six diseases: diphtheria, pertussis, tetanus, measles, poliomyelitis, and tuberculosis (Hadler and others 2004; Mitchell and others 2013). The fulcrum of the EPI program is the fixed health facility, where parents bring their children to be immunized.

The immunization visit has been expanded into the well-child visit, where the contact with the health system is used to add other preventive interventions (for example, vitamin A and growth monitoring). Vaccination is also delivered in many low- and middle-income countries (LMICs) through modes and mechanisms outside the well-child visit, such as mobile outreach clinics, supplemental immunization activities as part of eradication and elimination campaigns, and mass vaccination for control of outbreaks.

VACCINE-PREVENTABLE DISEASES: EPIDEMIOLOGY, BURDEN, AND VACCINES

This section describes the epidemiology, burden, and vaccines available for vaccine-preventable diseases among children in LMICs. The section is divided into the six original EPI vaccines, new and underutilized vaccines introduced since 2000, and vaccines that might become more widely used in young children during the next decade (summarized in annex table 10A.2).

Original EPI Vaccines

Bacille Calmette-Guérin Vaccine

Tuberculosis is caused by the bacterium *Mycobacterium tuberculosis* and is spread from person to person through

the air; it primarily causes disease in the lung, although it can spread to many parts of the body. Infection with *M. tuberculosis* may lie dormant for years. In 2012, the WHO estimated a global burden of 8.6 million cases and 1.3 million deaths due to tuberculosis; 55,000 of these were in children under age five years, 95 percent of which occurred in LMICs. Co-infection with human immunodeficiency virus (HIV) greatly increases the risk of developing active tuberculosis. The treatment of tuberculosis worldwide is becoming more complicated because of the rise of multidrug-resistant strains (Bloom and others, forthcoming; Connelly Smith, Orme, and Starke 2013; WHO 2015a).

BCG vaccine is a live-attenuated strain of a related mycobacterium, *Mycobacterium bovis*, originally isolated from an infected cow and attenuated through repeated passage. BCG is most effective against tuberculous meningitis and disseminated (miliary) tuberculosis. However, BCG vaccination does not prevent *M. tuberculosis* infection in childhood, when most infections occur, or reactivation of latent infection and pulmonary tuberculosis later in life, which is the principal source of community transmission (WHO 2004). In 2012, BCG was included in routine infant immunization schedules in 159 of 194 WHO member states; worldwide coverage was estimated to be 90 percent in 2012 (WHO, UNICEF, and World Bank 2002). Approximately 100 million infants receive BCG annually; more than 4 billion people have been vaccinated (Connelly Smith, Orme, and Starke 2013). The 100 million BCG vaccinations given worldwide to infants in 2002 prevented approximately 30,000 cases of tuberculous meningitis and 11,000 cases of miliary tuberculosis (Trunz, Fine, and Dye 2006).

Vaccination is recommended for all infants in countries with high tuberculosis disease burden and infants at high risk of exposure in low-burden countries. Because it is a live-attenuated vaccine, BCG is not recommended for immunocompromised children, including those with congenital severe combined immunodeficiency syndrome and those with symptomatic HIV infection.

Tuberculosis will not be eliminated without new, more effective tuberculosis vaccines (Connelly Smith, Orme, and Starke 2013). For the prevention of severe childhood diseases, a single BCG dose is recommended as soon as possible after birth (WHO 2004). BCG is the only vaccine in the EPI program routinely administered by intradermal injection, which requires specific injection supplies and health care worker training. BCG is produced by a large number of countries using different vaccine seed strains, which may contribute to the variability in effectiveness observed in different studies.

Diphtheria, Tetanus, and Pertussis Vaccine

Despite progress, these three bacterial diseases of infancy and early childhood remain endemic in some countries. Diphtheria is a respiratory illness characterized by membranous inflammation of the upper respiratory tract caused by toxin-producing *Corynebacterium diphtheriae* and is transmitted through respiratory droplets and coughing. Before vaccination, an estimated 1 million cases and 50,000–60,000 deaths occurred annually (Walsh and Warren 1979). In 2008, only 7,000 cases of diphtheria were reported; more than 85 percent of these occurred in India (WHO and UNICEF 2014). Tetanus is caused by a toxin produced by *Clostridium tetani*, a ubiquitous organism found in the soil and transmitted through contamination of wounds or unsterile procedures, including care of the umbilical cord. Neonatal tetanus is mostly present in LMICs, resulting in an estimated 34,481 deaths in 2015 in children in LMICs, which account for 99 percent of all under-five tetanus deaths worldwide (Liu and others 2016). Pertussis, or whooping cough, is a highly communicable respiratory illness caused by *Bordetella pertussis* and characterized by paroxysmal cough that may last for many weeks. Estimates from the WHO suggest that about 63,000 children died from this disease in 2008, 95 percent of them in LMICs (Black and others 2010).

DTP vaccines are composed of inactivated diphtheria and tetanus toxins (referred to as toxoids) and pertussis antigens, either killed, whole-cell *Bordetella pertussis* or purified antigens (acellular pertussis [aP] vaccine). Whole-cell pertussis acts as a potent adjuvant that improves the immune response to diphtheria and tetanus toxoids, but periodic boosting is required because of waning immune responses; waning may occur more quickly with aP vaccines (Edwards and Decker 2013). DTP vaccines combined with hepatitis B and *Haemophilus influenzae* type b (Hib) antigens are widely used in LMICs, while combination vaccines with aP are common in upper-middle- and high-income countries. Because the risk of pertussis complications is highest in infants too young to be vaccinated, maternal vaccination is a strategy that could protect young infants (CDC 2011).

DTP vaccine coverage is an important indicator of immunization program performance. Initiatives to strengthen routine immunization services often monitor progress as measured by coverage with the third DTP dose (DTP3) in infancy, which requires multiple immunization visits in the first year of life. The difference between coverage with the first versus the third DTP dose, often called *dropout*, measures loss to follow-up and challenges to completion of infant vaccinations. Many newer vaccines, including pneumococcal, meningococcal, and rotavirus vaccines, have adapted to DTP

immunization schedules to reach the maximum number of children during scheduled immunization visits.

DTP vaccines are included in routine childhood immunization programs in all 194 WHO member states. Global DTP3 coverage rose from 20 percent in 1980 to 84 percent in 2013 (WHO and UNICEF 2014), preventing 76,000 deaths from diphtheria and 1.6 million deaths from pertussis annually. In conjunction with improved maternal immunization against tetanus, the vaccines prevented approximately 408,000 deaths from tetanus (WHO 2013a). Despite increased coverage, more than 20 million infants remained unvaccinated in 2013 (WHO and UNICEF 2014). More than 80 percent of these children live in Gavi-eligible countries. If these countries achieved and maintained their DTP3 coverage at 90 percent between 2015 and 2020, 439,000 deaths and 16 million cases of pertussis could be averted during the 10 years from the scale-up (Stack and others 2011).

Polio Vaccine

The goal of universal polio vaccination is eradication. In 1988, when the Global Polio Eradication Initiative was established, poliomyelitis crippled more than 350,000 children each year, with transmission of wild poliovirus serotypes (1, 2, and 3) reported from 125 countries (WHO 2014c). From January to December 2015, only 66 cases of wild poliovirus type 1 were reported worldwide, compared with 359 cases in January to December 2014, and no cases of wild poliovirus had been reported on the African continent for 12 months; wild type 2 polioviruses have not been identified since 1999; and the last case of wild type 3 poliovirus occurred in 2012 (Global Polio Eradication Initiative 2013; WHO 2014b).

Implementation of routine childhood immunization and supplemental immunization activities with oral polio vaccine (OPV) containing attenuated polioviruses of all three types substantially decreased cases in LMICs and eliminated poliovirus circulation in the WHO regions of the Americas, Europe, Western Pacific, and South-East Asia. Clinical trials showed that three doses of OPV were needed for greater than 90 percent protection against paralytic poliomyelitis. However, the immune response was lower among children in LMICs, requiring more vaccine doses to achieve the high levels of population immunity necessary for elimination (Estívariz and others 2012; Grassly and others 2007). In 2014, the WHO recommended that all countries using OPV include at least one dose of inactivated polio vaccine (IPV) in their routine immunization schedule (WHO 2014c). Most immunization schedules in LMICs include a three-dose primary polio immunization schedule, and many include booster doses in the second year of life. For high-risk countries, the WHO recommends four doses beginning as soon as possible after birth, with at least one dose of IPV at age 14 weeks if only one IPV dose is given.

There are several steps to the Polio Eradication and Endgame Strategic Plan 2013–2018, and this transition in polio vaccination strategy has several phases. First, all OPV-using countries should introduce at least one dose of IPV (containing inactivated polioviruses of all three types) to boost immunity to poliovirus type 2 (WHO 2014b). Then, trivalent OPV will be replaced with more immunogenic bivalent OPV containing type 1 and 3 viruses. IPV introduction will pave the way for future total cessation of all OPV use after eradication has been achieved. Most high-income countries adopted routine childhood immunization with IPV to prevent rare cases of paralytic polio caused by OPV. However, achieving high coverage with IPV will require strengthening of routine immunization services.

Measles Vaccine

Measles is one of the most contagious diseases of humans (Fine and Mulholland 2013). It is caused by a paramyxovirus, manifesting as a febrile rash illness, which can result in multiple life-threatening complications, including pneumonia, diarrhea, and encephalitis. In 2000, measles was the leading vaccine-preventable cause of childhood deaths and the fifth leading cause of under-five mortality; that year, measles alone accounted for 5 percent of the estimated 10.9 million deaths among children under age five years (Strebel and others 2012). By 2010, measles-related deaths had declined by 75 percent following accelerated measles control activities in Sub-Saharan Africa and other regions (Simons and others 2012); declines in measles-related deaths accounted for almost 10.1 percent of overall declines in childhood mortality from 2000 to 2015 (Liu and others 2016). Further progress is expected as countries implement measles elimination strategies; as of 2014, all six WHO regions had established target dates for measles elimination.

Measles vaccination can prevent illness and death directly among vaccinated persons and indirectly among unvaccinated persons as a result of decreased transmission. In countries with ongoing transmission of measles and high risk of measles among infants, the WHO recommends vaccination at age nine months when protection provided by maternal antibody wanes and seroconversion rates improve among infants. In countries with low rates of measles transmission, the WHO recommends the first dose of vaccine at age 12 months to take advantage of higher seroconversion rates achieved at this age (Strebel and others 2012).

Between 1980 and 2011, global measles vaccination coverage rose from 18 percent to 84 percent globally (WHO 2013d; WHO, UNICEF, and World Bank 2002).

In one analysis, a projected 624 million children in Gavi-eligible countries would be vaccinated with one dose of measles-containing vaccine between 2011 and 2020, averting 10.3 million deaths relative to a hypothetical scenario in which countries were not administering measles vaccine (Lee and others 2013).

Because of its high risk of contagion, high levels of immunity are needed to interrupt measles transmission. A two-dose strategy is deemed essential for measles elimination, to immunize children who missed the first dose and protect up to 15 percent of children who do not seroconvert after primary immunization (WHO 2013d). Childhood immunization schedules in many countries include two doses. In countries with poor access to preventive services, the second opportunity for measles vaccination is most often provided through nationwide supplementary immunization activities or mass campaigns.

New and Underutilized Vaccines or Vaccine Strategies Supported by Gavi

Table 10.1 summarizes the large impact of vaccination for averting death and reducing disease burden in 73 countries receiving support from Gavi, with a focus on 10 new and previously underutilized vaccines. Expected impact is shown separately for vaccinations administered from 2001 to 2012 and vaccinations forecasted to be administered from 2013 to 2020. The total expected impact is shown as estimated numbers of persons immunized, as well as future deaths and DALYs averted. Estimates of future deaths and DALYs averted are based on a comparison of the number of deaths and DALYs expected over the lifetime of vaccinated cohorts relative to a hypothetical scenario in which the cohorts do not receive the vaccinations in question.

Hepatitis B Vaccine

Hepatitis B vaccine is included in routine infant immunization schedules to prevent serious disease and death later in life caused by chronic infection with hepatitis B virus, a member of the hepadnavirus family. Hepatitis B virus is a blood-borne pathogen that may also be transmitted sexually. Hepatitis B, one of five viruses known to cause hepatitis in humans, is responsible for most of the worldwide hepatitis burden: more than 2 billion people have been infected with hepatitis B virus, and 360 million have become chronically infected (WHO 2010b).

Table 10.1 Impact of Vaccination: Children Immunized and Deaths Averted in 73 Gavi-Supported Countries, Based on Strategic Demand Forecast Version 9

	Estimates for 2001–12			Projections for 2013–20		
	Children immunized	Deaths averted	DALYs averted	Children immunized	Future deaths averted	Future DALYs averted
Hepatitis B	377,000,000	3,400,000	99,000,000	480,000,000	3,700,000	109,000,000
Haemophilus influenzae type B	160,000,000	830,000	52,000,000	440,000,000	1,800,000	126,000,000
Japanese encephalitis (campaign)	83,000,000	19,000	1,000,000	71,000,000	9,000	1,100,000
Japanese encephalitis (routine)	21,000,000	6,000	840,000	93,000,000	20,000	3,300,000
Measles (routine 2nd dose)	71,000,000	90,000	6,000,000	350,000,000	220,000	14,000,000
Measles (campaign)	1,000,000,000	2,800,000	167,000,000	800,000,000	1,900,000	117,000,000
Meningitis A (campaign)	103,000,000	140,000	7,700,000	215,000,000	310,000	14,000,000
Meningitis A (routine)	n.a.	n.a.	n.a.	70,000,000	6,000	430,000
Pneumococcus	11,000,000	70,000	4,900,000	260,000,000	1,500,000	105,000,000
Rotavirus	4,000,000	4,000	320,000	230,000,000	380,000	24,000,000
Rubella (campaign)	105,000,000	20,000	1,800,000	650,000,000	190,000	18,000,000
Rubella (routine)	21,000,000	5,000	500,000	210,000,000	50,000	5,300,000
Yellow fever (campaign)	70,000,000	260,000	8,000,000	140,000,000	170,000	4,400,000
Yellow fever (routine)	84,000,000	540,000	21,000,000	120,000,000	570,000	23,000,000

Sources: Children immunized derived from the World Health Organization–United Nations Children's Fund Estimates of National Immunization Coverage and United Nations Population Division; vaccine introduction and scale-up scenario based on Gavi Strategic Demand Forecast Version 9; future deaths averted derived from Lee and others (2013); future DALYs averted derived from personal communication with S. Ozawa.
Note: Gavi = Gavi, the Vaccine Alliance; n.a. = not applicable; DALY = disability-adjusted life year.

Chronic hepatitis B virus infection is the leading cause of cirrhosis and cancer of the liver, which result in approximately 600,000 deaths annually (Goldstein and others 2005). Hepatitis B virus transmission may occur prenatally and during early childhood, adolescence, and adulthood. Vaccination is more than 95 percent effective in infants and more than 72 percent effective in preventing perinatal transmission. Vaccination must be part of a comprehensive prevention strategy. Humans are the only reservoir of hepatitis B virus, making disease elimination possible (WHO 2010b).

Modern hepatitis B vaccines containing recombinant hepatitis B virus surface antigen (HBsAg) were introduced in 1986 (Van Damme and others 2013). The WHO has recommended routine infant vaccination against hepatitis B since 1992. In 2013, hepatitis B vaccine was included in routine infant immunization schedules in 94 percent of 194 WHO member states. Infant immunization schedules include at least three doses of hepatitis B vaccine, which may be combined with other antigens, such as DTP and *Haemophilus influenzae* type b. In 2013, worldwide coverage with three doses of hepatitis B vaccine was estimated to be 81 percent. In countries with a high prevalence of hepatitis B virus infection, the WHO recommends administering the first dose within 24 hours of birth to prevent perinatal transmission. In 2013, 93 countries included hepatitis B birth dose in their routine immunization schedules, with global coverage estimated to be 38 percent. Better birth dose coverage and monitoring are needed; timely delivery of birth dose should be a performance measure of immunization programs (WHO 2013h).

Haemophilus influenzae Type b Vaccine

Haemophilus influenzae is a Gram-negative bacterium surrounded by a polysaccharide capsule, which is a major virulence factor. While six serotypes (a, b, c, d, e, f) and unencapsulated strains cause disease—including meningitis, pneumonia, septicemia, epiglottitis, cellulitis, septic arthritis, osteomyelitis, and otitis media (mainly due to unencapsulated *H. influenzae*)—Hib was the leading cause of meningitis in children under age five years in most countries before widespread vaccination (Bennett and others 2002). The mean case fatality rate (CFR) of Hib meningitis was 67 percent (44 percent to 75 percent) in Sub-Saharan Africa and 43 percent (23 percent to 55 percent) globally. In 2000, before widespread Hib vaccination, Hib caused an estimated 371,000 deaths (Watt and others 2009). By 2008, Hib vaccines were used in 136 countries, and estimated deaths had fallen to 203,000 (Black and others 2010; WHO 2013b).

Evidence from several clinical trials of Hib conjugate vaccine demonstrated the importance of Hib in causing severe pneumonia; Hib accounted for 25 percent of severe pneumonia in The Gambia and 22 percent in Chile (Levine and others 1999; Mulholland and others 1997). Hib pneumonia rates are higher than Hib meningitis rates; consequently, pneumonia accounted for the majority (79 percent) of the approximately 200,000 Hib-related deaths worldwide in children ages 1–59 months in 2010 (WHO 2013h).

The multiple formulations of Hib conjugate vaccines include several different conjugated proteins and combination vaccines, such as the most widely used pentavalent vaccine (DTP–Hepatitis B–Hib). Hib conjugate vaccines are more than 80 percent effective against Hib meningitis, sepsis, and bacteremic pneumonia; in most Sub-Saharan African countries that have introduced Hib vaccine into the national program, Hib disease has virtually disappeared (Adegbola and others 2005; Cowgill and others 2006; WHO 2006b). However, Hib vaccines likely have reduced efficacy in HIV-infected children, and evidence from South Africa suggests a booster dose might be required (Mangtani and others 2010). In many settings, three doses of Hib vaccine in infancy may control the disease and do not appear to increase rates of *H. influenzae* disease caused by serotypes other than type b (Ribeiro and others 2007; Zanella and others 2011). By 2013, 186 countries had introduced Hib vaccines, and as of 2014, all 73 Gavi countries vaccinated against Hib alongside hepatitis B, diphtheria, tetanus, and pertussis through the pentavalent vaccine as part of their routine infant immunization programs.

Future needs include introduction of Hib vaccine into countries that have not yet introduced it, particularly in Asia.

Pneumococcal Conjugate Vaccine

Streptococcus pneumoniae, the pneumococcus, is a Gram-positive encapsulated bacterium commonly found in the respiratory tract. Pneumococci are surrounded by polysaccharide capsules that confer serotype; more than 90 pneumococcal serotypes have been identified, although a limited number cause most disease. Pneumococcal disease is the leading bacterial cause of pneumonia in children and also causes meningitis and septicemia. The CFR of pneumococcal disease worldwide is approximately 5 percent (range 4 percent to 9 percent), but it is more than double that rate in Sub-Saharan Africa (CFR 11 percent; range 7 percent to 18 percent) (O'Brien and others 2009). About 90 percent of pneumococcal deaths are due to pneumonia. Pneumococcal meningitis, though rare, has a higher CFR of 59 percent (range 27 percent to 80 percent); it can be as high as 73 percent in Sub-Saharan Africa. Before widespread pneumococcal conjugate vaccination, pneumococcus caused an

estimated 826,000 deaths (O'Brien and others 2009) in 2000, and 541,000 deaths among children younger than age five years worldwide in 2008 (WHO 2013b).

Pneumococcal conjugate vaccines are at least 80 percent effective against meningitis, septicemia, and bacteremic pneumonia (Lucero and others 2009); like Hib vaccines, pneumococcal conjugates likely have reduced efficacy in HIV-infected children (Klugman and others 2003). Two pneumococcal conjugate vaccines are currently commercially available; one contains the conjugated polysaccharides of 10 serotypes, and the other contains 13 serotypes. Evidence suggests that declines in disease caused by vaccine serotypes with pneumococcal conjugate vaccine use may be partially offset by increased disease due to nonvaccine serotypes (referred to as *serotype replacement*); however, according to one meta-analysis of invasive pneumococcal disease in high-income countries, childhood vaccination resulted in 50 percent reductions in pneumococcal disease overall, despite some serotype replacement (Feikin and others 2013). Introduction of pneumococcal conjugate vaccine into Asian countries has lagged Gavi-supported introduction into Africa.

Rotavirus Vaccine

Rotavirus, a member of the reovirus family, causes watery diarrhea that can lead to dehydration and death. It is the leading cause of childhood diarrhea-related mortality worldwide (Parashar and others 2003), responsible for an estimated 453,000 deaths in 2008 (Tate and others 2012). Rotavirus accounts for 35 percent to 50 percent of acute severe diarrhea in children, varying by region (Mwenda and others 2010), with the highest proportions in children younger than age one year (Kotloff and others 2013). Unlike bacterial and parasitic causes of diarrhea, the occurrence of rotavirus diarrhea is not higher in settings with poor water, sanitation, and hygiene. A recent study of moderate-to-severe diarrhea in seven low-income settings found a CFR from rotavirus presenting to a health facility of 2.5 percent (Kotloff and others 2013). This figure is higher in areas without good access to health care (Feikin and others 2012) (see Keusch and others 2016, chapter 9 in this volume).

Two rotavirus vaccines are commercially available (WHO 2009). Both have been efficacious in randomized controlled trials in low-income settings, with efficacies generally ranging from 50 percent to 80 percent against rotavirus diarrhea; the lowest efficacy was seen in lower-socioeconomic, higher-mortality countries (Armah and others 2010; Madhi and others 2010). Nonetheless, because of higher rates of disease in these countries, the number of serious rotavirus infections prevented is likely to be higher, and the WHO strongly recommends rotavirus vaccine use in these countries (WHO 2009). Lower-cost rotavirus vaccines are still needed (Bharat Biotech 2011). Infants who receive rotavirus vaccines have a slightly elevated risk of a rare but serious condition called *intussusception*, which can result in potentially fatal bowel obstruction, although increased incidence of intussusception is small relative to the overall impact of the vaccine (Patel and others 2012; Patel and others 2011). Future needs include development of vaccines with improved efficacy in high-burden countries and introduction of rotavirus vaccine into high-burden Asian countries.

Rubella Vaccine

The rubella virus, a member of the togavirus family, is one of the most teratogenic viruses known. In the absence of vaccination, rubella is a common cause of febrile rash illness in children, often misdiagnosed as measles. Infection of susceptible women early in pregnancy can result in miscarriage, fetal death, or a constellation of congenital defects known as congenital rubella syndrome (CRS) in up to 90 percent of infected infants. The incidence of rubella and CRS has been reduced in many high-burden countries following implementation of rubella vaccination strategies.

The goal of rubella vaccination in high-burden countries is to prevent the substantial disease burden associated with CRS. It is estimated that more than 100,000 CRS cases occur worldwide each year (Vynnycky, Gay, and Cutts 2003). Through 2013, 137 countries have included rubella-containing vaccines in national immunization schedules; the introduction of rubella vaccination in Asia and Sub-Saharan Africa lags other regions (WHO 2011b). Live-attenuated rubella virus vaccines were first licensed in 1970, but they were not included in EPI programs because of concerns that suboptimal vaccine coverage could delay age at natural rubella virus infection and result in higher incidence among women of childbearing age, paradoxically increasing the risk of CRS. Since 2011, the WHO has recommended introduction of rubella vaccination strategies as part of measles control and elimination activities, taking advantage of the availability of combined measles-rubella (MR) and measles-mumps-rubella (MMR) vaccines (WHO 2011b).

The preferred strategy for the introduction of rubella vaccination is to begin with MR/MMR vaccine in a campaign targeting a wide range of ages, in combination with universal childhood vaccination (Reef and Plotkin 2013). The first dose of combined MR vaccine can be delivered at age 9 months or 12 months, depending on the level of measles virus transmission (WHO 2011b). The effectiveness is at least 95 percent, even at age 9 months; only

one dose of rubella vaccine is required to achieve rubella elimination if high coverage is achieved (WHO 2011b).

Meningococcal Meningitis Serogroup A Conjugate Vaccine

Neisseria meningitidis, also referred to as the meningococcus, is a Gram-negative encapsulated bacterium transmitted by respiratory droplets that can cause severe bloodstream infections and meningitis; it is the leading cause of bacterial meningitis in many LMICs. Explosive outbreaks of meningococcal meningitis occur with high attack rates and case fatality across broad age ranges. Six *N. meningitidis* serogroups (A, B, C, W, X, Y) cause almost all cases, although prevalence varies temporally and geographically. Sub-Saharan African countries from Senegal to Ethiopia in a zone referred to as *the meningitis belt* have experienced frequent and devastating epidemics of meningococcal meningitis, most often caused by serogroup A meningococcal strains. From 1993 to 2012, countries in the meningitis belt reported nearly 1 million meningitis cases, including 100,000 deaths (WHO 2013f).

Meningococcal vaccines prevent diseases caused by specific serogroups: vaccines against serogroups A, C, W, and Y contain purified polysaccharide alone or conjugated to carrier proteins (based on diphtheria or tetanus toxoids), while serogroup B vaccines contain outer membrane vesicles extracted from outbreak strains with the addition of recombinant proteins. Conjugate vaccines provide better long-lasting immunity, particularly in children younger than age two years, and indirect protection of unvaccinated groups through the reduction of disease transmission. Meningococcal conjugate vaccines have been introduced into routine immunization programs in many high-burden countries. In 2010, a serogroup A meningococcal conjugate vaccine developed by the Meningitis Vaccine Project, with funding from the Bill & Melinda Gates Foundation, was licensed for use in countries in the meningitis belt (LaForce and Okwo-Bele 2011). In the Sub-Saharan African meningitis belt, the WHO recommends mass vaccination of the population ages 1–29 years (WHO 2011a), a highly effective strategy for prevention of serogroup A meningococcal disease (Novak and others 2012), followed by routine childhood vaccination with a single dose at age 9–18 months (WHO 2015b).

Yellow Fever Vaccine

Yellow fever is a viral hemorrhagic fever that was one of the most feared epidemic diseases in the world before vaccination. Despite the availability of an effective vaccine, yellow fever continues to cause an estimated 84,000 to 170,000 severe cases annually, with 29,000 to 60,000 deaths (WHO 2013e). Most reported cases and deaths occur in 31 endemic Sub-Saharan African countries with a total population of 610 million, more than 33 percent of whom live in urban settings. Since the 1980s, yellow fever has reemerged in some areas or appeared for the first time in others.

Yellow fever vaccines contain live-attenuated virus and have been used since the 1930s (Monath and others 2013). Routine infant immunization against yellow fever is only recommended in 44 at-risk countries and territories, of which 35 included yellow fever vaccine in their routine infant immunization schedules in 2013. A single dose of yellow fever vaccine at age nine months or later is assumed to provide lifelong immunity.

Japanese Encephalitis Vaccine

Japanese encephalitis (JE) is the most common cause of viral encephalitis in Asia (WHO 2013c). JE virus, a flavivirus, is transmitted by mosquitoes in natural cycles involving domestic pigs or water birds; human disease is common in areas with rice cultivation and pig farming. Of the estimated 67,900 annual cases in the 24 endemic countries, 51,000 (75 percent) occur in children ages 0–14 years, resulting in about 10,000 deaths and 15,000 cases of long-term neuropsychiatric sequelae (Campbell and others 2011). Reported cases underestimate geographic distribution of risk because of underreporting and occurrence of disease in less than 1 percent of human infections (Halstead, Jacobson, and Dubischar-Kastner 2013). In recent decades, outbreaks have occurred in several previously nonendemic areas.

The WHO recommends the introduction of JE immunization through EPI programs in areas where JE constitutes a public health problem (WHO 2006a). In 2012, JE vaccines were used in immunization programs in 11 (46 percent) of 24 at-risk countries (WHO 2013c). The most effective strategy for controlling JE has been to conduct wide age-range (catch-up) vaccination followed by routine infant immunization. In upper-middle- and high-income economies—including Japan; the Republic of Korea; and Taiwan, China—routine immunization since 1965 using inactivated, mouse-brain-derived vaccine has successfully controlled the disease (Halstead, Jacobson, and Dubischar-Kastner 2013). However, disadvantages of the mouse-brain vaccine include the need for multiple doses, frequent boosting, and high prices (WHO 2006a). In 2013, the WHO and the United Nations Children's Fund approved a live-attenuated JE vaccine from a Chinese manufacturer based on the SA 14-14-2 strain, which induces protection for several years after one or two doses (WHO 2013g). Approval of the live-attenuated JE vaccine should increase access in endemic countries.

Additional and Future Vaccines with Potential Public Health Impacts in Young Children

Malaria Vaccine

Approximately 198 million malaria cases and 584,000 malaria deaths occurred globally in 2013; most deaths were in young children living in Sub-Saharan Africa (WHO 2015c). *Plasmodium falciparum* is the most virulent of the five *Plasmodium* species that cause human malaria. The RTS,S/AS01 candidate malaria vaccine is a partially effective vaccine that targets the pre-erythrocytic stage of the *P. falciparum* parasite resulting in a reduction in the number of clinical malaria episodes experienced. RTS,S/AS01 recently underwent testing in a large phase 3 clinical trial, the final stage before licensure. In total, 15,460 children and young infants participated in the trial, which was conducted at 11 sites in seven Sub-Saharan African countries across a wide range of malaria transmission levels (RTS,S Clinical Trials Partnership 2015). Among children ages 5–17 months at first vaccination followed for a median of 48 months, RTS,S/AS01 vaccine efficacy against clinical malaria was 37 percent (95 percent confidence interval 32–41) when the primary vaccination series of three doses administered monthly was followed by a booster given 18 months after the primary vaccination series, and 28 percent (95 percent confidence interval 23–33) when no booster was given. Vaccine efficacy was lower in young infants who received the primary vaccination series coadministered with EPI vaccines beginning at ages 6–12 weeks: 26 percent (95 percent confidence interval 20–32) with a booster and 18 percent (95 percent confidence interval 12–24) without. Despite modest efficacy estimates, the impact was substantial: 1,774 cases of clinical malaria were averted per 1,000 children vaccinated when a booster was administered; 1,363 cases were averted without a booster. The number of cases averted per 1,000 young infants was 983 in those who received a booster and 558 in those who did not. Meningitis and febrile seizures were reported more frequently in those who received the RTS,S/AS01 primary vaccination series than in those in the comparator group.

In July 2015, the European Medicines Agency issued a positive scientific opinion on RTS,S/AS01 for the prevention of malaria in children in Sub-Saharan Africa. Subsequently, the WHO's Strategic Advisory Group of Experts on Immunization and the Malaria Policy Advisory Committee reviewed the evidence on RTS,S/AS01 efficacy and safety as well as other relevant information surrounding vaccine implementation. In October 2015, the WHO advisory groups recommended the implementation of the vaccine through pilot projects designed to better understand how well the vaccine can be implemented and to further assess the relationship of safety signals to the vaccine (WHO 2015d). The WHO is considering these recommendations and was expected to provide guidance in early 2016. RTS,S/AS01 may become the first malaria vaccine licensed for use in children in Sub-Saharan African countries (RTS,S Clinical Trials Partnership 2015).

Influenza Vaccine

Influenza viruses are orthomyxoviruses that cause respiratory illness, ranging from mild febrile illness to severe pneumonia. Because influenza viruses change rapidly, vaccines are reformulated and delivered annually through routine immunization or seasonal campaigns. Influenza viruses infecting humans are transmitted person to person, mostly by droplets and aerosols from the respiratory secretions of infected people. Influenza viruses cause seasonal influenza epidemics, mostly in the winter months in temperate climates, with less distinct seasonality in the tropics. Influenza has an annual attack rate of 5 percent to 10 percent in adults and 20 percent to 30 percent in children. When complicated by subsequent bacterial pneumonia, influenza infections can have high mortality rates. In general, the role of influenza in LMICs has been underestimated. A review suggests that 6.5 percent of hospital admissions for respiratory illness among Sub-Saharan African children were due to influenza (Gessner, Shindo, and Briand 2011). Another meta-analysis estimates that 28,000 to 111,500 influenza-associated deaths occur annually in children, with 99 percent occurring in LMICs (Nair and others 2013).

Licensed influenza vaccines include inactivated or live-attenuated influenza type A and B viruses. Inactivated influenza vaccines (IIVs) are administered by injection; live-attenuated virus vaccines are delivered as nasal spray. Only IIV is licensed for children younger than age two years. Two doses of influenza vaccine given four weeks apart are recommended during the first season a child is vaccinated. Vaccine effectiveness varies annually according to protection provided against circulating influenza viruses, but in general, vaccination has provided significant protection in children (Jefferson and others 2012), although few studies of vaccine effectiveness have been conducted among children in LMICs (WHO 2012b). Maternal influenza immunization has gained support as a way of protecting infants too young to be vaccinated against influenza disease. A study in Bangladesh shows that giving influenza vaccine to pregnant women led to an efficacy of 63 percent against lab-confirmed influenza and 29 percent against febrile respiratory illness in their infants' first six months of life (Zaman and others 2008). Maternal influenza vaccination with IIV is now recommended in some countries and is being studied in LMICs as a method for preventing influenza in young infants (CDC 2013;

WHO 2012a). No cost-effectiveness data on the use of influenza vaccine in LMICs are available. The WHO suggests that countries make their respective decisions on influenza vaccines based on local disease burden, resources, capacity, and other health priorities (WHO 2012a).

Oral Cholera Vaccine

Cholera is caused by ingestion of toxigenic serogroups (O1 and O139) of *Vibrio cholerae* bacteria, leading to diarrhea, dehydration, and rapid death. Periodically, new strains of *V. cholerae* emerge to cause pandemics. In 1970, the seventh pandemic strain appeared in Sub-Saharan Africa, where it is now endemic and accounts for the majority of cholera mortality (Mintz and Guerrant 2009). Cholera incidence and mortality is greatest in children (Ali and others 2012; Deen and others 2008), who account for 50 percent of all cholera deaths. Globally, cholera kills at least 45,000 children under age five years annually; this number is likely to be twice as high when considering out-of-hospital mortality (Ali and others 2012; Sack 2014). In 2010, cholera was introduced into Haiti following a massive earthquake, causing more than 500,000 cases (Barzilay and others 2013). Although the cholera CFR can be less than 1 percent in settings with good access to health care and proper treatment, these conditions rarely exist in most LMICs, where CFRs often exceed 5 percent and can be as high as 50 percent during outbreaks (Gaffga, Tauxe, and Mintz 2007; WHO 2010a).

There are two WHO-approved oral cholera vaccines, which contain formalin-inactivated or heat-killed whole-cell *V. cholerae*. One vaccine showed greater than 80 percent effectiveness against cholera for at least the first six months after administration (Clemens, Sack, and Ivanoff 2001; van Loon and others 1996); the second showed 67 percent effectiveness against cholera during the first two years of follow-up among children vaccinated at ages 1–4 years (Sur and others 2011).

These vaccines were cost-effective in a crowded city like Kolkata, India, at US$1 per dose; they would likely be cost-effective in other settings, such as Sub-Saharan Africa, if significant herd protection occurs with the vaccine, as has been hypothesized. In 2010, the WHO recommended use of oral cholera vaccines in addition to other preventive strategies, such as provision of safe water, in cholera-endemic countries or areas likely to experience outbreaks, with priority for vaccination given to children in settings of limited vaccine supply (Jeuland and others 2009; Longini and others 2007; WHO 2010a). For vaccination during large outbreaks like those in Haiti and Zimbabwe (Ahmed and others 2011; Barzilay and others 2013), the WHO plans to create an emergency stockpile of 2 million doses of cholera vaccine (Martin, Costa, and Perea 2012).

COST AND COST-EFFECTIVENESS OF VACCINATIONS

Cost

Despite the relatively low cost of traditional EPI vaccines, more than 20 million infants did not receive the third dose of DTP-containing vaccine in 2013; the majority of these children lived in five countries: the Democratic Republic of Congo, Ethiopia, India, Nigeria, and Pakistan. National EPI programs have evolved in the past 15 years; the WHO universally recommends vaccines against 11 different diseases for infants—tuberculosis, hepatitis B, polio, diphtheria, tetanus, pertussis, Hib, pneumococcus, rotavirus, measles, and rubella. As more countries increase coverage of new and underutilized vaccines, the cost of fully immunizing a child increases.

The costs of delivering existing and new vaccines to beneficiary populations can be challenging to quantify, especially over time with the introduction of new vaccines. Early studies of the principal EPI vaccines estimated the cost of fully immunizing a child to range from US$10 to $US20, depending on the region and place of vaccine delivery (Brenzel and Claquin 1994). Using more recent immunization financing data after the advent of Gavi (from Financial Sustainability Plans), the cost of fully immunizing a child in 50 of the poorest Gavi-eligible countries was estimated to increase from US$6.00 to US$17.50 per infant with the addition of hepatitis B and Hib vaccines and increased coverage (Lydon and others 2008). An updated estimate in Gavi-eligible countries based on financial data from the WHO (Comprehensive Multi-Year Plans) increased the cost to US$23 per infant for 2008–11, increasing to a projected cost of US$42 per infant in 2016 (Brenzel, Young, and Walker 2015). There was substantial variability by WHO region, with Europe having the highest costs and South-East Asia and the Western Pacific regions the lowest; more than one-third of the total projected cost of vaccination from 2011 to 2020 (US$57.5 billion) is expected to be spent in India, Nigeria, and Pakistan (Gandhi and others 2013). Non-vaccine delivery costs can account for nearly half of the total costs of vaccination (Brenzel 2015; Gandhi and others 2013; Lydon and others 2008).

As highly effective yet more expensive vaccines become available, many countries with already-strained resources will have to find the right balance between increasing coverage with available vaccines in often hard-to-reach areas or introducing new vaccines into the national immunization schedule.

A systematic review of cost-effectiveness analyses from 44 published articles of 23 vaccines in 51 countries finds that vaccines cost less than US$100 per DALY averted in more than half of the articles, and less than

US$1,000 per DALY averted in nearly 90 percent of the articles (Horton, Wu, and Brouwer 2015).

Table 10.2 shows the relative cost-effectiveness of different vaccines using the accepted metric of cost per DALY averted. For comparison, if the cost per DALY averted for an intervention is less than per capita gross national income (GNI), it is very cost-effective; if less than three times per capita GNI, it is cost-effective (WHO 2001). Those vaccines in the third column are very cost-effective in upper-middle-income countries, as long as cost per DALY does not exceed US$4,087, the cutoff in 2012 between lower-middle- and upper-middle-income countries, per the World Bank. A more detailed analysis of cost-effectiveness of vaccines is presented in chapter 17 in this volume (Horton and Levin 2016).

Direct Social and Economic Benefits

Immunization coverage has traditionally been monitored using DTP3 coverage or measles vaccine coverage as indicators. Most countries now deliver DTP through newer combination vaccines—for example, as of 2014, all 73 Gavi countries were using the pentavalent vaccine that combines Hib and hepatitis B with DTP. However, even though DTP3 coverage in 2013 was high—84 percent globally and 76 percent in the 73 Gavi countries—fewer than 5 percent of children received all 11 WHO-recommended immunizations. Clearly, immunization platforms are effective in reaching many children with some vaccines, but large gaps in protection remain.

The timeliness of vaccination is critical, particularly for diseases for which most mortality occurs in the first six months of life, for example, pertussis and Hib. Additionally, timely vaccination ensures maximal herd immunity and protects those who are too young to be fully vaccinated (Akmatov and others 2008; Clark and Sanderson 2009; Patel and others 2011). A review of immunization timeliness in 45 countries found a median delay of six weeks for receipt of DTP3; in countries with the greatest delays, 25 percent of children received DTP3 at least 19 weeks late (Clark and Sanderson 2009).

Fully immunized children who receive on-time vaccinations obtain the greatest protection and greatest reduction of the risk of mortality in the first six months of life from preventable childhood diseases. Such immunization also conveys broader direct social and economic benefits, leading to greater adult productivity and contributing to economic development. Directly averting illness through immunization can lead to lower medical costs and missed wages by caretakers. Vaccines that prevent diseases that cause disabilities have improved school enrollment and attainment rates (Simmerman and others 2006) and cognitive ability linked to test scores (Bloom, Canning, and Seiguer 2011), thereby increasing a population's human capital in the long term (Bloom, Canning, and Jamison 2004). Ozawa and others (2012) quantify the impact of vaccination on health care cost saving, care-related productivity gains, and outcome-related productivity gains.

Most of the evidence on the economic benefit of vaccines has been for health care savings and care-related productivity gains that directly affect the finances of

Table 10.2 Approximate Range of Cost-Effectiveness of Various Childhood Vaccines, Various Contexts (2012 U.S. dollars per DALY averted)

< US$100/DALY[a]	US$100 to <US$1,036/DALY[b]	Over US$1,036/DALY[c]
Original EPI-6: BCG, DTP, measles, polio	*Haemophilus influenzae* type B	Cholera (final price point pending)
Hepatitis B	Yellow fever, where endemic	Pneumococcus, low-child-mortality countries
Pneumoccocus, high-child-mortality countries	Japanese encephalitis, where endemic	Rotavirus, low-child-mortality countries
Rotavirus, high-child-mortality countries	Pneumococcus, medium-child-mortality countries	
	Rotavirus, medium-child-mortality countries	
	Meningitis A, where endemic	

Source: For details on sources and references, see table 17.1 of chapter 17 of this volume (Horton and Levin 2016).
Note: EPI = Expanded Program on Immunization; BCG = Bacille Calmette-Guérin; DALY = disability-adjusted life year; DTP = diphtheria, tetanus, and pertussis. For vaccines, cost-effectiveness is sensitive to vaccine price as well as variability in underlying disease burden by country.
a. Vaccines in the first column are very cost-effective in all low-income countries because cost per DALY averted is less than per capita gross national income (GNI) of even the poorest low-income country (World Bank definition of "low-income country" is per capita GNI of less than US$1,035 in 2012 and in 2012 the per capita income of the poorest low-income country was approximately US$250).
b. Vaccines in the second column are very cost-effective in all lower-middle-income countries (World Bank definition of "lower-middle-income country" is per capita GNI in 2012 ranging between US$1,036 and US$4,085).
c. Vaccines in the third column may be very cost-effective in upper-middle-income countries (World Bank definition of "upper-middle-income country" is per capita GNI in 2012 ranging between US$4,086 and $12,615).

the vaccinated child's household. These savings can greatly affect household economies and health system expenditures in resource-strained settings. Scaling up coverage with vaccines against pneumococcal disease, Hib, rotavirus, pertussis, measles, and malaria to 90 percent over 10 years could save US$6.2 billion in treatment costs and avert US$1.2 million in caretaker lost wages in 73 Gavi-supported countries (Stack and others 2011).

Indirect Social and Economic Benefits

The wider indirect economic impact of vaccines on societies lies beyond vaccinated households. Many childhood vaccines have proven to have additional value by protecting persons who are still susceptible to infection, including those who are too young and too old to be vaccinated, through a mechanism referred to as herd protection, herd immunity, or community immunity. This indirect impact of vaccination has been shown for many vaccines, including those against measles, Hib, influenza, meningococcus, and pneumococcus (Fine, Eames, and Heymann 2011; Fine and Mulholland 2013). When the disease burden is large in adults, more disease is possibly prevented among unvaccinated adults than among vaccinated children, as has been shown in the United States with pneumococcal conjugate vaccine (CDC 2005).

- Between 1995 and 2001, the seven routine vaccines in the United States resulted in an estimated savings of US$10 billion in direct costs and US$43 billion in societal costs (Zhou and others 2005).
- Averting morbidity and mortality by scaling up the six original EPI vaccines to 90 percent over 10 years could increase productivity in 73 Gavi-eligible countries by US$145 billion over the lifetime of vaccinated children (Stack and others 2011).
- Behavior-related productivity gains due to vaccination include the effects of longer life expectancies (Bloom, Canning, and Weston 2005; Meij and others 2009) and alleviated poverty (Bawah and others 2010) on societal productivity. By 2020, the investments by Gavi could result in internal rates of return of 18 percent (Bloom, Canning, and Weston 2005).
- Finally, preventing outbreaks through immunization saves societies the opportunity cost of reacting to outbreaks after they have occurred. For example, modeling (Khan 2008) shows that introducing IPV in the 148 countries using OPV would save US$163 million in poliomyelitis outbreak containment costs per year over 10 years.

CONCLUSION

Vaccines have been one of the most important forces in reducing childhood mortality during the past 40 years. With the advent of new vaccines and the promise of others, immunizations have the potential to further drive down childhood mortality and deliver broader health and economic benefits. Remaining challenges need to be addressed in the coming decade:

- Progress in controlling and eliminating many diseases—including polio, measles, rubella, meningococcal meningitis, yellow fever, and JE—will increasingly depend on coordination between routine immunization services and supplementary immunization activities, including mass vaccination. It is important to ensure that supplementary immunization activities are planned and implemented in such a manner that they strengthen routine immunization programs, wherever possible.
- Immunization programs need to reduce disparities in levels of effective vaccination coverage and to monitor progress in fully immunizing children.
- Additional resources are required for immunization programs as new vaccines become available and national governments assume greater shares of program costs.
- The number of immunization visits required to ensure full immunization coverage of all recommended vaccines has increased relative to the original EPI schedule, which served as the foundation for delivering many interventions. These schedule changes lead to logistical and programmatic challenges and require enhancements to health workforce and program capacities. They also present opportunities to strengthen the delivery of other services in coordination with vaccination.
- Innovations are needed to make vaccine delivery easier, such as heat-stable vaccines that do not require cold chain, and to provide alternate delivery mechanisms, such as microneedle patches.
- Programs need to work to improve immunization timeliness and take advantage of opportunities to provide multiple interventions.
- Newer vaccines (for example, rotavirus vaccine and malaria vaccine) may be less effective than traditional EPI vaccines but may prevent a substantial burden of disease, given the high incidence of these diseases (Gessner and Feikin 2014). The evaluation process for vaccines will likely need to shift from an exclusive focus on vaccine efficacy to a focus on the vaccine-preventable disease burden.

Despite these challenges, immunization will remain central to childhood disease prevention, and the well-child visit will continue to serve as the axis upon which preventive activities evolve. The unprecedented momentum in global immunizations during the past decade must be sustained. To maximize the health and economic well-being of populations, it is especially important to fully immunize children with all recommended vaccines and to effectively use immunization as a platform to deliver other cost-effective and life-saving services as part of a comprehensive well-child approach.

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