Volume 2: Reproductive, Maternal, Newborn and Child Health

Chapter 10. Vaccine Preventable Diseases in children

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Boxes:
Figures:
Maps:
Tables: 3
Word count: 15,320 (including tables and references)
Annexes: Annex __A supplemental material for DCP3 website (600 words). Includes Annex Table 1 and Table 2

Outline

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, the two leading causes of child mortality, account for two million deaths annually; vaccination has the potential to prevent 59 percent of pneumonia deaths and 29 percent of diarrheal deaths (Fischer Walker, Munos, and others 2013). Other leading causes of childhood deaths are already preventable through available and effective vaccines, such as measles and meningitis, or may become preventable through effective vaccines in the near future, such as malaria (Agnandji and others 2011 Liu, Johnson, and others 2012). Forecasts for vaccine use in the 73 countries supported by the GAVI Alliance project 17.7 million deaths averted in children under age five years as a result of vaccinations administered from 2011-20 (Lee, Franzel, and others 2013).

In addition to the clear health benefits, vaccination has been one of the most cost-effective public health interventions (Brenzel, Wolfson, 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 Immunizations (EPI) was US$205 in South Asia and Sub-Saharan Africa; it was US$7-US$16 for estimated cost per disability adjusted life year (DALY) (Brenzel, Wolfson, and others 2006). New vaccines, although more expensive, have also been determined to be cost-effective in GAVI-eligible countries (Atherly, Lewis, and others 2012; Sinha, Levine, and others 2007).

In this chapter, we describe the epidemiology and burden of vaccine-preventable diseases and provide estimates of the value of vaccines in terms of deaths averted.

Methods

We describe vaccines in three categories:

- Vaccines among the six original EPI antigens: Bacille Calmette-Guerin (BCG); diphtheria, tetanus, and pertussis (DPT); measles, and polio
- Vaccines classified as new, underutilized, or regional, and supported by the GAVI Alliance since its inception in 2000
- New vaccine strategies that might be introduced as routine immunization 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 search of relevant updated websites on vaccines. For the impact of vaccination of 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 the GAVI Alliance and the Bill and Melinda Gates Foundation to estimate the impact of vaccinations administered in the 73 GAVI-supported countries (Annex A, Annex Table 1). [insert URL for DCP3 website location when available].

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, Cochi, and others 2004; Plotkin and Vidor 2008). The fulcrum of the EPI program is the fixed health facility, where parents bring their children to be immunized.

Since its inception, the immunization visit has been expanded into the well-child visit, where the contact with the health system was utilized to add other preventive interventions (for example, Vitamin A and growth monitoring). Vaccination is also delivered in many LICs and LMICs

through modes and mechanisms outside of 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, Vaccines

In this section, we describe the epidemiology, burden and vaccines available for vaccine preventable diseases among children in low and low-middle income countries. We have divided the section into the six original EPI vaccines, vaccines introduced since the inception of GAVI in 2000, and vaccines that might become more widely used over the next decade.

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 in children under age five years, 95 percent of which occurred in LICs and LMICs.

BCG 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 tuberculosis meningitis and disseminated (miliary) tuberculosis. However, BCG vaccination does not prevent *M. tuberculosis* infection in childhood, when most infections occur, nor reactivation of latent infection and pulmonary tuberculosis later in life, which is the principal source of community transmission (WHO 2004). Vaccination with BCG is recommended for routine childhood immunization in most LICs and LMICs with a high tuberculosis burden (WHO 2004). In 2012, BCG was included in routine infant immunization schedules in 159 of 194 WHO member states; worldwide coverage was estimated at 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 tuberculosis meningitis and 11,000 cases of miliary tuberculosis (Trunz, Fine, and others 2006).

In countries with a low tuberculosis burden, vaccination is recommended for infants at high risk of exposure. BCG is not recommended for immunocompromised children and those with symptomatic HIV infection.

For the prevention of severe childhood diseases, a single 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. Some evidence indicates that BCG is effective against leprosy (Rodriques and Lockwood 2011) and that non-specific effects of BCG on the immune system might reduce childhood mortality from other diseases (Garly, Bale, and others 2001; Roth, Jensen, and others 2004). Ongoing efforts seek to develop a more effective tuberculosis vaccine.

Diphtheria, Tetanus, and Pertussis Vaccine

Despite progress in combating these three common bacterial diseases of infancy and early childhood, they remain endemic in some countries. Major outbreaks, including a resurgence of diphtheria in the 1990s in the Russian Federation, have occurred.

Diphtheria is a respiratory illness characterized by membranous inflammation of the upper respiratory tract caused by toxin-producing *Corynebacterium diphtheriae* and transmitted through respiratory droplets and coughing. Before vaccination, an estimated 1 million cases and 50,000 to 60,000 deaths occurred annually (Walsh and Warren 1979). Tetanus is caused by 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 the most common presentation in LICs and LMICs, resulting in an estimated 56,000 deaths annually in children (WHO and UNICEF 2013). 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 LICs and LMICs (Black, Cousens, and others 2008).

DTP vaccines are composed of inactivated diphtheria and tetanus toxins (referred to as *toxoids*) and pertussis antigens, either killed, whole-cell *Bordetella pertussis* (wP), 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 due to waning immune responses; waning may occur more quickly with acellular pertussis vaccines (Edwards and Decker 2013). DTP vaccines combined with hepatitis B and Hib antigens are widely used in LICs and LMICs, while combination vaccines with acellular pertussis are common in HICs and upper-middle-income countries (UMICs). The use of combination vaccines containing DTP or DTaP with inactivated polio vaccine (IPV) is increasing as LICs and LMICs introduce IPV.

DTP vaccine coverage is an important indicator of immunization program performance. Initiatives to strengthen routine immunization services often monitor progress in terms of 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 *drop-out*, measures loss to follow-up and challenges to complete 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 has risen from 20 percent in 1980 to 83 percent in 2012 (WHO and UNICEF 2013), which prevented 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 the increased coverage, 23 million infants remained unvaccinated in 2012 (WHO and UNICEF 2013). Approximately 87 percent of these children live in GAVI-eligible LICs and LMICs. If these countries were able to raise their DTP3 coverage from 2010 levels to 90 percent

by 2015 and continue at 90 percent through 2020, then 439,000 deaths and 16 million cases of pertussis could be averted over the 10 years from the scale-up (Stack, Ozawa, and others 2011).

Polio

Poliomyelitis, a leading cause of disability in children, is caused by three serotypes (1, 2 and 3) of poliovirus. The goal of universal polio vaccination is eradication. Since the creation of the Global Polio Eradication Initiative in 1988, progress has been made. 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 LICs and LMICs and eliminated poliovirus circulation in the WHO regions of the Americas, Europe, and the Western Pacific. 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 LICs and LMICs, requiring more vaccine doses to achieve the high levels of population immunity necessary for elimination. Most immunization schedules in LICs and 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.

In 2012, 223 cases of wild-type polio types 1 and 3 were identified worldwide, the lowest number to date; wild type 2 polioviruses have not been identified since 1999 (Global Polio Eradication Initiative 2013; WHO 2014a). However, resurgence of wild type 1 in the horn of Africa and the Middle East led to an increase in the number of cases in 2013.

Once global eradication is achieved, the use of OPV will be phased out and immunization programs that continue to vaccinate against polio will use inactivated polio vaccine (IPV). First, the WHO recommended that all OPV-using countries introduce at least one dose of IPV (containing inactivated polioviruses of all three types) to boost immunity to poliovirus type 2 (WHO 2014a). 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 cessation of all OPV use. Most HICs and some LICs and LMICs 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 immunizations services. Strategies are also needed to increase access to affordable IPV.

Measles

Measles is caused by a paramyxovirus virus, manifesting as a febrile rash illness, which can result in multiple life-threatening complications, including encephalitis, pneumonia, and diarrhea. In 2000, measles was the leading vaccine-preventable cause of childhood deaths and the fifth leading cause of under-five mortality; measles alone accounted for 5 percent of the estimated 10.9 million deaths among children under age five years that year (Strebel, Papania, and others 2012). By 2010, measles deaths had declined by 75 percent following accelerated measles control activities in Sub-Saharan Africa and other regions (Simons, Ferrari, and others 2012); declines in measles deaths accounted for almost 20 percent of overall declines in childhood mortality from 2000-10 (Liu, Johnson, and others 2012). Further progress is expected as countries implement measles elimination strategies; as of 2014, all six WHO regions have established target dates for measles elimination (Strebel and others 2013).

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 nine months of age when protection provided by maternal antibody wanes and seroconversion rates improve among infants (Strebel and others 2013). In countries with low rates of measles transmission, the WHO recommends the first dose of vaccine at 12 months to take advantage of higher seroconversion rates achieved at this age (Strebel and others 2013).

In 1980, vaccination coverage was approximately 18 percent globally. Between 2000-11, coverage of at least one dose of a measles vaccine rose from 73 percent globally to 84 percent, lowering measles deaths 71 percent to approximately 158,000 in 2011 (WHO 2013g; WHO, UNICEF, and others 2002). In one analysis, a projected 624 million children in GAVI-eligible countries would be vaccinated with one dose of measles containing vaccine 2011-20, averting 10.3 million deaths relative to a hypothetical scenario in which countries were not administering measles vaccine (Lee, Franzel, and others 2013).

In 2009, the WHO recommended two doses of measles vaccine for all countries to protect up to 15 percent of children who do not seroconvert after primary immunization (WHO 2013g). The second dose may be offered either at a well-child visit through routine services or periodically through mass campaigns. 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. The impact of a second measles dose in GAVI-eligible countries is shown in Table __.2.

Table 3 Impact of Vaccination in Terms of Children Immunized and Deaths Averted in 73 GAVI Supported Countries, Based Strategic Demand Forecast V7

	Estimates for 2000-2012			Projections for 2013-2020		
	Children immunized	Future deaths averted	Deaths averted per thousand vaccinated	Children immunized	Future deaths averted	Deaths averted per thousand vaccinated
HepB	372,000,000	3,200,000	8.5	470,000,000	3,800,000	8.1
Hib	160,000,000	800,000	5.0	435,000,000	1,900,000	4.4
JE (campaign)	-	-	-	91,000,000	21,000	0.2
JE (routine)	-	-	-	147,000,000	43,000	0.3
Measles (routine 2nd dose)	27,000,000	24,000	0.9	195,000,000	225,000	1.2
Measles (campaign)	--	--	--	660,000,000	1,000,000	1.5
Men A (campaign)	107,000,000	111,000	1.0	149,000,000	155,000	1.0
Men A (routine)	--	--	--	40,000,000	3,000	0.1
Pneumo	11,000,000	86,000	7.9	280,000,000	1,800,000	6.5
Rotavirus	4,000,000	7,000	1.7	280,000,000	480,000	1.7
Rubella (campaign)	--	--	--	506,000,000	345,000	0.7
Rubella (routine)	--	--	--	140,000,000	64,000	0.5
Yellow fever	92,000,000	18,000	0.2	150,000,000	30,000	0.2
HPV	37,000	400	10.9	36,000,000	575,000	15.8

Source:

Notes: *Estimated cohort of surviving infants in GAVI eligible countries in 2012 is approximately 75 million

[change table number to 2]

New and Underutilized Vaccines Supported by GAVI

The number of GAVI-eligible countries using each GAVI-supported vaccine by the end of 2012, the number of children immunized in these countries, and the deaths averted by each vaccine are summarized in Annex A, Tables 1 and 2.

Hepatitis B

Hepatitis B vaccine is included in routine infant immunizations 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 become chronically infected (WHO 2010b). 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, Zhou, and others 2005). Hepatitis B virus transmission may occur prenatally, 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 2012, hepatitis B vaccine was included in routine infant immunization schedules in 93 percent of 194 WHO member states and 97 percent of 73 GAVI-eligible countries. 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 2012, worldwide coverage with three doses of hepatitis B vaccine was estimated at 79 percent. In countries with a high prevalence, the WHO recommends administering the first dose within 24 hours of birth to prevent perinatal transmission. In 2012, 52 percent of 181 countries with hepatitis B vaccination, representing 65 percent of the global birth cohort, included a birth dose in their national immunization program. Birth dose coverage has lagged behind coverage for the complete infant series; strategies are needed to improve timeliness for maximum benefit (WHO 2013j).

Haemophilus Influenzae Type B

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, septicaemia, epiglottitis, cellulitis, septic arthritis, and osteomyelitis—*H. influenzae* type b (Hib) was the leading cause of meningitis in children under age five years in most countries prior to widespread vaccination (Bennett, Platonov, and others 2002). The mean case-fatality rate (CFR) of Hib meningitis was 67 percent (44 percent–75 percent) in Sub-Saharan Africa and 43 percent (23 percent–55 percent) globally.

Much of the high CFR is due to lack of access to care; the CFR for Hib meningitis when treated promptly with antibiotics is 5 percent to 8 percent. Evidence from several clinical trials of Hib

conjugate vaccine shed new light on the importance of Hib in causing severe pneumonia; approximately five cases of Hib pneumonia occur for each case of Hib meningitis (Mulholland, Levine, and others 1999). Hib accounted for 25 percent of severe pneumonia in The Gambia and 22 percent in Chile (Levine, Lagos and others 1999; Mulholland, Hilton, and others 1997). While Hib was not considered to be as an important cause of disease in much of Asia, a vaccine trial in Indonesia revealed that Hib did cause a significant amount of meningitis and pneumonia (Gessner, Sutanto, and others 2005). Globally, the case-fatality ratio for Hib pneumonia is estimated to be 4 percent (2 percent to 7 percent) and higher in Sub-Saharan Africa, where it is 8 percent (5 percent to 14 percent) (Watt, Wolfson, and others 2009). Despite having a lower CFR than Hib meningitis, Hib pneumonia rates are higher than Hib meningitis rates. Consequently, pneumonia accounted for the majority (79 percent) of the approximately 200,000 Hib deaths worldwide in children ages 1 month to 59 months in 2010 (Watt, Wolfson, and others 2009; WHO 2013j).

Although antibodies to the Hib polysaccharide capsule confer immunologic protection, infants respond poorly to polysaccharide vaccines. Only when polysaccharide was successfully conjugated to a protein carrier in the late 1980s were infants able to mount an effective immune response to Hib vaccine. Currently, there are multiple formulations of Hib conjugate vaccines that 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, Secka, and others 2005; Cowgill, Ndiritu, 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, Mulholland, 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, Lima, and others 2007; Zanella, Bokermann, and others 2011).

Pneumococcal Conjugate

Streptococcus pneumoniae, the pneumococcus, is a gram-positive bacterium commonly found in the respiratory tract. It is the leading bacterial cause of pneumonia in children and more rarely causes meningitis and septicemia. The case fatality ratio 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, 7 percent to 18 percent) (O'Brien, Wolfson, and others 2009). Ninety 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. In 2008, *Streptococcus pneumoniae* caused an estimated 541,000 deaths among children younger than age five years worldwide; a separate estimate using different methodology estimated 411,000 deaths in 2010, and likely accounts for 7 percent of the total global burden of deaths (O'Brien, Wolfson, and others 2009; WHO 2013c).

Pneumococci are surrounded by polysaccharide capsules that confer serotype; there are over 90 serotypes, although a limited number cause most disease. Pneumococcal capsular polysaccharides provide serotype-specific protection in adults but are poorly immunogenic in infants. Conjugation of pneumococcal polysaccharides to carrier proteins resulted in effective

vaccines for infants. The first pneumococcal conjugate vaccine was introduced in the United States in 2000 (Whitney, Farley, and others 2003). Pneumococcal conjugate vaccines are at least 80 percent effective against meningitis, septicemia, and bacteremic pneumonia (Lucero, Dulalia, and others 2009); like Hib vaccines, pneumococcal conjugate likely have reduced efficacy in HIV-infected children (Klugman, Madhi, 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 non-vaccine serotypes (referred to as *serotype replacement*); however, according to one meta-analysis of invasive pneumococcal disease in HICs, childhood vaccination resulted in 50 percent reductions in pneumococcal disease overall, despite some serotype replacement (Feikin, Kagucia, and others 2013).

Rotavirus

Rotavirus, a member of the reovirus family, causes watery diarrhea that can lead to dehydration and death, and is the leading cause of childhood diarrhea mortality worldwide (Parashar, Hummelman, and others 2003). Rotavirus accounts for 35 percent to 50 percent of acute severe diarrhea in children, varying by region (Mwenda, Ntoto, and others 2010; Tate, Burton, and others 2012). Rotavirus causes a larger proportion of diarrhea in children younger than age one year than among older children (Kotloff, Nataro, 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, Nataro, and others 2013). This figure is higher in areas without good access to health care (Feikin, Laserson, and others 2012).

Two rotavirus vaccines are commercially available (WHO 2009b). 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, Sow, and others 2010; Madhi, Cunliffe, and others 2010). Nonetheless, because of higher rates of disease in these countries, the number of serious rotavirus infections prevented is likely higher, and the WHO strongly recommends rotavirus vaccine use in these countries (WHO 2009b). Other rotavirus vaccines are being developed, including one with comparable efficacy tested in India, which reportedly will be available at US$1 per dose (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, Clark, and others 2012; Patel, Lopez-Collada, and others 2011).

Rubella

The rubella virus, a member of the togavirus family, is a common cause of febrile rash illness in children, when most infections occur in the absence of vaccination. Infection of susceptible women early in pregnancy often results in miscarriage, fetal death, or a constellation of congenital defects known as *congenital rubella syndrome* (CRS). Many rubella infections are asymptomatic, challenging control efforts. Clinically, rubella is often misdiagnosed as measles. In 2009, the global measles and rubella laboratory network found rubella to be the cause of 15

percent of rash illness episodes with specimens submitted for testing. The incidence of rubella and CRS has been reduced in many LICs and LMICs following implementation of rubella vaccination strategies.

The goal of rubella vaccination in LICs and LMICs is to prevent the substantial public health burden associated with congenital rubella syndrome. Mathematical modeling has estimated that over 100,000 CRS cases occur worldwide each year (Vynnycky, Gay, and others 2003). As of December 2009, a total of 130 of 193 WHO Member States included rubella-containing vaccines in national immunization schedules; the introduction of rubella vaccination in Asia and Sub-Saharan Africa lags behind other regions (WHO 2011b). Live, attenuated rubella virus vaccines were first licensed in 1970, but they were not included in EPI programs due to 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 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 together with immediate introduction of MR/MMR vaccine into the routine program (Reef and Plotkin 2013). The first dose of combined measles-rubella vaccine can be delivered at age nine months or 12 months, depending on the level of measles virus transmission (WHO 2011b). The effectiveness is at least 95 percent, even at age nine months; only one dose of rubella vaccine is required to achieve rubella elimination if high coverage is achieved (WHO 2011b).

Countries in four WHO regions have established goals for elimination or control of rubella and CRS; in 2012, the World Health Assembly endorsed a plan to eliminate rubella and CRS from five WHO regions by 2020 (CDC 2013b). In 2013, the GAVI began providing support for rubella in the form of the measles-rubella vaccine.

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 LICs and 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 and 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 1993-2012, countries in the meningitis belt reported nearly 1 million meningitis cases, including 100,000 deaths (WHO 2013b).

Meningococcal vaccines prevent diseases caused by specific serogroups: polysaccharide vaccines (A, C, W, Y), polysaccharide–protein conjugate vaccines contain capsular polysaccharides (A, C, W, Y) conjugated to carrier proteins (based on diphtheria or tetanus toxoids), while serogroup B vaccines contain outer membrane vesicles extracted from outbreak strains. Conjugate vaccines are preferred over polysaccharide vaccines due to superior direct

immunogenicity, particularly in children younger than two years of age, and indirect protection of unvaccinated population through reduced meningococci carriage (herd effect.) Meningococcal conjugate vaccines have been introduced into routine immunization programs in many LICs and LMICs. In 2010, a serogroup A meningococcal conjugate vaccine developed by the Meningitis Vaccine Project, with funding from the Bill and 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 one to 29 years (WHO 2011a), a highly effective strategy for prevention of serogroup A meningococcal disease (Novak, Kambou, and others 2012).

Yellow Fever

Yellow fever is a viral hemorrhagic fever that was one of the most feared epidemic diseases in the world prior to vaccination. Despite the availability of an effective vaccine, yellow fever is estimated to cause 84,000 to 170,000 severe cases annually, with 29,000 to 60,000 deaths (WHO 2013h). 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 re-emerged 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, Gershman, and others 2013). Routine infant immunization against yellow fever is only recommended in 48 at-risk countries; in 2012, 36 (75 percent) included yellow fever vaccine in routine infant immunization schedules. 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 2013d). 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 67,900 annual JE 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, Hills, and others 2011). Reported cases underestimate geographic distribution of risk due to underreporting and occurrence of disease in less than 1 percent of human infections (Halstead, Jacobson, and Dubischar-Kastner 2013). In recent decades, outbreaks of JE 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 2013d). The most effective strategy to control JE has been conducting wide age-range (catch-up) vaccination followed by routine infant immunization. In HICs and UMICs—including Japan; the Republic of Korea; and Taiwan, China—routine immunization since 1965 using inactivated, mouse-brain derived vaccine has successfully controlled JE (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 UNICEF 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 (2006a). Approval of the live-attenuated JE vaccine should increase access in endemic countries (WHO 2013i).

Additional and Future Vaccines with Potential Public Health Impacts in Children

Malaria

Plasmodium falciparum caused an estimated 219 million cases of malaria and 660,000 deaths in 2010; most deaths occurred in young children living in Sub-Saharan Africa (WHO 2012b). Marked gains have been made in malaria control during the past decade, with the scale-up of insecticide-treated mosquito nets (ITNs), the expansion of indoor residual spraying (IRS), and the introduction of highly effective artemisinin-containing antimalarial therapy. However, those gains are threatened by emerging insecticide and drug resistance (Dondorp, Nosten, and others 2009; Protopopoff, Matowo, and others 2013).

Plasmodium falciparum, the most virulent of the five *Plasmodium* species that cause human malaria, is transmitted by the *Anopheles* mosquito. The pre-patent period (the interval from first infection to the time when parasites are detectable in the peripheral blood) is nine to 10 days. The RTS,S/AS01 candidate malaria vaccine, developed by GlaxoSmithKline, is the most advanced malaria vaccine in clinical development, and the only malaria vaccine candidate that is undergoing phase 3 clinical trials, the final stage prior to licensure (WHO 2014c). RTS,S/AS01, which targets the pre-erythrocytic stage of the *P. falciparum* parasite, is being evaluated in 15,460 children at 11 sites in seven Sub-Saharan African countries across a wide range of malaria transmission levels. RTS,S/AS01 is a partially effective vaccine and delays or reduces the number of clinical malaria episodes experienced. Vaccine efficacy against clinical and severe malaria during 12 months following the primary vaccination series (three doses administered monthly) in children ages five to 17 months at first vaccination was 56 percent and 47 percent, respectively. Thus, clinical and severe malaria episodes were reduced by approximately 50 percent. Vaccine efficacy was lower in young infants who received the vaccine co-administered with EPI vaccines beginning at age six to 12 weeks; in this age group, vaccine efficacy was 31 percent against clinical malaria and 37 percent against severe malaria. The trial is ongoing; information on safety, duration of efficacy, and the role of a booster will be collected during the remainder of the trial. Based on the full set of findings, the WHO will issue a policy recommendation on the public health use of RTS,S in 2015 (Moorthy, Hutubessy, and others 2012), and the vaccine then may become the first malaria vaccine licensed for use in children in Sub-Saharan countries.

If the vaccine is found to be safe and effective, the next critical questions prior to implementation will be whether the vaccine will be cost-effective and affordable. Cost-effectiveness analyses have been limited because the trial is not yet completed, questions remain on how the vaccine will be distributed; the manufacturer has not yet set a price for the vaccine. However, a modeling exercise predicted that a partially effective pre-erythrocytic vaccine such as RTS,S/AS01, provided in co-administration with the EPI vaccines, would be most cost-effective in areas of moderate to low malaria transmission (Maire, Shillcutt, and others 2011).

Influenza

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 LICs and LMICs has been underestimated. A recent review suggested that 6.5 percent of hospital admissions for respiratory illness among Sub-Saharan African children was due to influenza (Gessner, Shindo, and others 2011). Another recent meta-analysis estimated that 28,000 to 111,500 influenza-associated deaths occur annually in children, with 99 percent occurring in LICs and LMICs (Nair, Simoes, and others 2013).

Licensed influenza vaccines include inactivated or live-attenuated influenza A and B viruses. Inactivated influenza vaccines (IIV) 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). Few studies of vaccine effectiveness have been conducted among children in LICs and LMICs (WHO 2012a). A study in Bangladesh showed 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 the first six months of life (Zaman, Roy, and others 2008). No cost-effectiveness data on the use of influenza vaccine in LICs and 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

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 younger than age five years annually; this number is likely to be double when considering out-of-hospital mortality (Ali and others 2012; Sack 2014). In October 2010, cholera was introduced following a massive earthquake into Haiti, causing over 500,000 cases (Barzilay, Schaad, and others 2013). Although the cholera CFR can be less than 1 percent in settings with good health-care seeking and proper treatment, these conditions rarely exist in most LICs and LMICs, where CFRs often exceed 5 percent and can be as high as 50 percent during outbreaks (Gaffga, Tauxe, and others 2007; WHO 2010a).

There are two WHO-approved oral cholera vaccines, which contain formalin-inactivated or heat-killed whole-cell *V. cholerae*.

- The first (WC-rBS, Dukurol), using killed whole-cell serogroup O1, contains a recombinant B-subunit of the cholera toxin, must be ingested with a bicarbonate buffer and is licensed in a two-dose schedule for persons age two years or younger; a booster is

suggested in children ages two to five years. WC-rBS has been shown to have high effectiveness for at least the first six months after administration (greater than 80 percent), but protection likely wanes after the first year (Clemens and others 2001; Van Loon and others 1996).

- The second oral cholera vaccine (WC, Shanchol), a bivalent vaccine including serogroups O1 and O139, lacks the B-subunit, does not require a buffer, and can be administered to persons age one year and older in a two-dose schedule. Effectiveness during the first two years of follow-up was 67 percent. Significant protection was evident in the second year of follow-up in children vaccinated at ages one to four years (Sur and others 2011). WC currently costs approximately US$1.85; WC-rBS is more expensive (BioSpectrum Bureau 2012).

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 given to vaccination of children in settings of limited supply (Jeuland and others 2009; Longini and ohers 2007; WHO 2010a). Due to vaccine supply constraints, the WHO plans to stockpile 2 million doses of cholera vaccine to be released to LICs and LMICs during large outbreaks (Martin and others 2012), like those in Haiti and Zimbabwe (Ahmed and others 2011; Barzilay and others 2013).

Cost of Vaccinations

Childhood immunization schedules are developed to provide all recommended vaccines by a specified age. As more vaccines become available, the cost of fully immunizing a child increases. By 2011, the cost of immunizing a child against the six original EPI antigens was an estimated US$4 in GAVI-eligible countries (Gandhi and others 2013). Despite the relatively low cost, almost 23 million infants do not complete routine immunizations each year; 63 percent of under-immunized children live in five countries: Ethiopia, India, Indonesia, Nigeria, and Pakistan.

In addition, disparities exist in vaccination status 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 DTP3 varied from 67 percent in the southeast to 9 percent in the northwest (NPC 2009). Disparities are largely driven by socioeconomic status; the poorest children, with the highest disease burden, are the least vaccinated (Cutts, Izurieta, and others 2013).

As new, more expensive vaccines, become available, many countries with already strained resources will have to choose between increasing coverage with available vaccines in often hard-to-reach areas or introducing new vaccines into the national immunization schedule. This decision is difficult to make because vaccine prices and per dose delivery costs can hide the rising costs of overall immunization systems. In 2000, the cost of fully immunizing a child in 50 of the poorest countries was estimated at US$6 (Lydon and others 2008). A recent analysis of reported government expenditures (from comprehensive Multi-Year Plans or cMYPs) showed that in five countries with the original EPI schedule, immunization cost approximately US$17

per fully immunized child (Brenzel 2012), despite procurement costs of less than US$1.50 (Gandhi and others 2013), due to costs of staffing and logistical support for vaccination.

Today, the WHO universally recommends vaccines against 11 different diseases for infants, including tuberculosis, hepatitis B, polio, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (Hib), pneumococcus, rotavirus, measles, and rubella. Although procurement and delivery costs for the vaccines against these diseases are approximately US$33 per child (Gandhi 2013), cMYP expenditure analysis places the program costs of countries that have introduced pneumococcal conjugate vaccine and pentavalent into their schedules closer to US$42 per fully immunized child (Brenzel 2012).

GAVI Alliance

The GAVI Alliance was launched in 2000 to increase access to immunization in poor countries. The GAVI Alliance is a public-private partnership involving the WHO, UNICEF, 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 (GAVI 2013); and the financial community. The GAVI Alliance supported 73 countries in 2014, based on eligibility criteria determined through per capita GNI.

Since its initial support for hepatitis B, Hib, and yellow fever vaccines, GAVI has expanded its support to additional vaccines, including those against pneumococcus, rotavirus, meningococcus serogroup A, measles-rubella, human papillomavirus (HPV), JE, and inactivated polio vaccine. GAVI has also approved a contribution to the global cholera stockpile for use in epidemic and endemic settings. From its inception through August 2013, GAVI has committed US$ 8.4 billion in program support until 2016 to LICs and LMICs; 80 percent has been committed to the purchase of vaccines (GAVI 2013). From 2000 through 2012, GAVI-supported vaccines have helped countries to vaccinate 390 million children through routine programs. Annex Table 1 shows the vaccines supported by GAVI in the 73 GAVI-eligible countries.

A further innovative financing mechanism called an Advanced Market Commitment (AMC) was established in 2007 to introduce and scale up the pneumococcal conjugate vaccine (Cernuschi and others 2011) through the GAVI Alliance. The AMC secured US$1.5 billion from six donor countries and the Bill & Melinda Gates Foundation, which allowed a financial commitment to purchase the vaccine for introduction and scale up in GAVI-supported countries at predetermined terms.

Financing of more expensive antigens will pose constraints upon donors, GAVI, and countries. As of January 2014, per capita gross national incomes in 17 GAVI-supported countries had risen above eligibility thresholds, resulting in a five-year transition period during which the countries finance an increasingly large share of their vaccines each year. Such countries need to mobilize domestic resources to sustainably finance their vaccines when they complete the graduation process.

The Fully Immunized Child and the Value of Vaccination

Immunization coverage has traditionally been measured through DTP3, or at times measles, as a single indicator vaccine. Most countries now deliver DTP through newer combination

vaccines—for example, as of the end of 2012, 70 of 73 GAVI-supported countries were using the pentavalent vaccine that combines Hib and hepatitis B with DTP. However, while DTP3 coverage in 2012 was high—84 percent globally and 73 percent in 73 GAVI-supported countries—fewer than 5 percent of children received all 11 WHO-recommended immunizations. Clearly, immunization platforms are effective in reaching many children one or more times in infancy, but large gaps in immunological protection remain. The success of immunization programs needs to be monitored in terms of fully vaccinated children, in addition to coverage with individual vaccines. Projections based on current forecasting by the GAVI Alliance indicate a rise in the proportion of fully immunized children from less than 5 percent in 2012 to 70 percent in 2030 (Jamison, Summers, and others 2013).

The timeliness of vaccination is also critical, particularly for diseases where 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, Kretzschmar, and others 2008; Clark and Sanderson 2009; Patel, Lopez-Collada, and others 2011). A review of immunization timeliness in 45 countries found a median delay of six weeks for DTP3; in countries with the greatest delays, 25 percent of children received DTP3 at least 19 weeks late (Clark and Sanderson 2009).

Fully immunizing children with all recommended vaccines also conveys broader social and economic benefits. Immunization can lead to more productive populations and contribute to a country's overall economic development. For example, directly averting illness through immunization can lead to lower medical costs, fewer missed wages, and greater household income. Vaccines that prevent diseases causing disabilities have improved school enrollment and attainment rates (Simmerman, Lertiendumrong, and others 2006) and cognitive ability linked to test scores (Bloom and others 2010), thereby increasing a population's human capital in the long-term (Bloom and others 2004).

Ozawa and colleagues (2012) broke these benefits into six different categories:

- Health care cost savings
- Care-related productivity gains
- Willingness to pay and value of statistical life
- Outcome-related productivity gains
- Behavior-related productivity gains
- Outbreak prevention savings.

Most of the evidence on the economic benefit of vaccines falls into the first two categories, which directly impact the finances of the vaccinated child's household. These savings can greatly affect household economies and health system expenditures in resource-strained settings. For example, 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 US$1.2 million in caretaker lost wages in 73 GAVI-supported countries (Stack, Ozawa, and others 2011). Many cost-effectiveness studies also include projections on the economic benefits of vaccination in a given setting.

Although limited, there have also been studies on the wider economic impact of vaccines on societies beyond the vaccinated household. Averting morbidity and mortality by scaling up the

six vaccines to 90 percent over 10 years could increase productivity in 73 GAVI-eligible countries by US$145 billion over the lifetime of the vaccinated cohort (Stack, Ozawa 2011). Behavior-related productivity gains due to vaccination include the effects of longer life expectancies (Bloom, Canning, and others 2005; Meij, De Craen, and others 2009) and alleviated poverty (Bawah 2010) on societal productivity. Finally, preventing outbreaks through immunization saves societies the opportunity cost of reacting to outbreaks after they have occurred. For example, Khan (2008) modeled that introducing the IPV in the 148 countries using oral polio vaccine (OPV) at the time would result in US$163 million in outbreak prevention savings per year over 10 years.

Some new vaccines will have lower efficacy than traditional EPI vaccines. For example, rotavirus and malaria vaccines have approximately 50 percent efficacy against severe disease in LICs and LMICs (Agnandji, Lell, and others 2011; Armah, Sow, and others 2010; D'Alessandro 2012; Madhi, Cunliffe, and others 2010). Nonetheless, the vaccine preventable disease for such vaccines is very high, given the high incidence of these diseases (Gessner and Feikin 2014). The evaluation process of vaccines is likely to be shifting away from an exclusive focus on vaccine efficacy to a focus on the vaccine preventable disease burden.

Cost-Effectiveness of Vaccination

Table __.3 shows the relative cost-effectiveness of different vaccines, using the accepted metric of cost to save one DALY. For comparison, if the cost per DALY for an intervention is less than the per capita Gross National Income (GNI), it is “very cost-effective” and if less than three times per capita GNI, it is “cost-effective” (World Bank 2014).

Vaccines in the first column are very cost-effective even in LICs; those in the second column are very cost-effective in all LMICs; those in the third column are very cost-effective in all UMICs, as long as cost per DALY does not exceed US$4,087, the cutoff in 2012 between LMICs and UMICs. The acceptance of a regime of tiered pricing for vaccines ─ whereby lower-income countries are eligible for the lowest prices through GAVI ─has improved the cost effectiveness of vaccines in LMICs and helped allow the expansion of EPI to include additional vaccines. This tiered pricing regime has been, in part, made possible by market arrangements guaranteeing specific volumes of vaccine purchase for manufacturers, in particular, by GAVI. A more detailed analysis of cost-effectiveness of vaccines is presented in chapter 17.

Table 4. Approximate Range of Cost-Effectiveness Of Various Childhood Vaccines in LMICs, Various Contexts (US$ 2012 per DALY).

< $100/DALY	$100-<$1036/DALY[a]	Over $1036/DALY
Original EPI-6 (BCG, DPT, measles, polio Hepatitis B (where endemic) Pneumococcus (at subsidized GAVI price), high mortality LMICs Rotavirus (at subsidized GAVI price), high mortality LMICs	Haemophilus influenzae B Yellow fever (at GAVI price, where endemic) Japanese encephalitis (at GAVI price) Pneumococcus (unsubsidized GAVI price, high and medium child mortality LMICs) Rotavirus (unsubsidized GAVI price, high and medium child mortality LMICs) Meningitis A	Cholera Typhoid Pneumococcus (discounted price but > GAVI price), low child mortality countries Rotavirus (discounted price but > GAVI price), low child mortality countries

Notes:
For details of sources and references see cost-effectiveness chapter.
[a] In 2012, the definition of low income countries was per capita GNI < $1036: World Bank, 2014.

[Change table number to 3]

Conclusions

Vaccines have been one of the most important forces in reducing childhood mortality over 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. Yet, remaining challenges need to be addressed over the coming decade.

- Progress in controlling and eliminating many diseases—including polio, measles, rubella, meningococcal meningitis, yellow fever, and Japanese encephalitis—will increasingly depend on coordination between routine immunization services and supplementary immunization activities, including mass vaccination.
- Immunization programs will need to work to reduce disparities in access to vaccines and to monitor progress in fully immunizing children.
- Additional resources will be 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 fully immunize children may be more than in the original EPI schedule, which served as the foundation for delivering many interventions. For example, second doses of measles require immunization visits in the second year of life, while HPV requires multiple contacts with school-aged children. These schedule changes will lead to logistical and programmatic challenges in countries and will require additional staff training.
- Programs will also need to work to improve immunization timeliness and take advantage of opportunities to provide multiple interventions.

Despite these challenges, immunization will remain the center of the prevention of disease in the well child, and the well-child visit will continue to serve as the axis upon which preventive activities evolve over the next few decades. 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.

Table __.1. Characteristics of Common Childhood Vaccines

Vaccine (common abbreviations)	Type of vaccine	Diseases prevented	No. countries with routine vaccination, 2012	No. (%) of 73 GAVI countries with routine vaccination, 2012	Schedule	Vaccine efficacy	Duration of immunity	Estimated deaths in children < 5 years, rounded to thousands (2012 unless indicated)	Source for deaths
Recommended vaccines for national immunization programs in all developing countries									
Bacille Calmette-Guérin (BCG)	Live-attenuated *Mycobacterium bovis*	Disseminated disease and meningitis caused by *M. tuberculosis*	159	69 (95%)	1 dose at birth	75-86%	Unknown; most efficacious in preventing severe childhood disease	55,000	WHO, 2014b
Diphtheria, Tetanus, Pertussis (DTP, DTwP or DTaP)	Diptheria toxoid, tetanus toxoid, killed whole cell (wP) or acellular (aP) *Bordatella pertussis*	Diphtheria, tetanus, pertussis	194	73 (100%)	3 doses age ≤6 months + boosters	70-90% pertussis; >95% tetanus; >87% diphtheria	5-10 years depending on natural boosting; waning of pertussis immunity more pronounced with acellular vaccine	Diphtheria 1,000; pertussis 63,000, tetanus 56,000	WHO, 2014b
Oral Polio (OPV)	Live-attenuated Sabin poliovirus type 1, 2, 3 (monovalent, bivalent [1,3] or trivalent)	Poliomyelitis	159	73 (100%)	At birth + 3 doses age ≤6 months + boosters	~90%	Presumed lifelong	<1	Global Polio Eradication Initiative

Inactivated Polio (IPV)	Inactivated wild poliovirus type 1, 2, 3 (trivalent)	Poliomyelitis	66	1 (1%)	3 doses age ≤6 months + boosters	80-90%		<1	Global Polio Eradication Initiative
Measles, Measles-containing vaccine (M, MCV)	Live-attenuated measles virus	Measles	194	73 (100%)	9-15 months, 1st dose; 15+ months 2nd dose	85-95%	Lifelong in most; some waning after one dose	101,000	WHO, 2014b
Haemophilus influenzae type b conjugate (Hib)	Hib polysaccharide-protein conjugate	Hib diseases (meningitis, pneumonia)	180	68 (93%)	3 doses age ≤6 months	>85% invasive disease	Unknown; possible waning in older children	203,000 (2008); 197,000 (2010)	Watt, 2009;WHO, 2013c
Hepatitis B (HB)	Recombinant hepatitis B surface antigen		181	71 (97%)	At birth + 2 or 3 doses age ≤6 months	75-95%	>15 years	5,000	WHO, 2014b
Pneumococcal conjugate (PCV)	Pneumococcal polysaccharide-protein conjugate (10- or 13-valent)	Pneumococcal diseases (meningitis, pneumonia)	88	23 (32%)	3 doses age ≤6 months, or 2 or 3 doses ≤6 months + booster 9-15 months	>70% vaccine-serotype invasive disease	At least through childhood	541,000 (2008); 411,000 (2010)	O'Brien 2009;WHO, 2013c
Rotavirus (RV)	Live-attenuated human reassortment or bovine pentavalent rotavirus	Rotavirus gastroenteritis	41	11 (15%)	2 or 3 doses age ≤6 months (different vaccines)	50-77% severe gastroenteritis	Unknown; possible waning in 2nd year of life	453,000 (2008); 193,000 (2010)*	Tate 2012; Walker 2013
Rubella, Rubella-containing vaccine (R, RCV)	Live-attenuated rubella virus	Rubella, congenital rubella syndrome	132	20 (27%)	1 dose age ≥9 months	95%	Lifelong in most; rare waning after one dose	30,000 (no year)	Cutts 1999;Lee 2013
Recommendations for certain regions or high-risk populations									

Meningococcal serogroup A conjugate (MenA)	Polysaccharide-protein conjugate	Meningococcal meningitis and disease due to serogroup A	12 of 25 high-risk countries	12 of 25 high-risk countries	Under evaluation	>95%	Under evaluation	10,000/year (all ages, 1993 to 2012)	WHO 2013b
Yellow Fever (YF)	Live-attenuated yellow fever virus	Yellow fever	37 of 48 high-risk countries	24 (33%)	1 dose age ≥9 months	90-98%	Presumed lifelong	29,000-60,000	WHO 2013h
Japanese Encephalitis (JE)	Live-attenuated japanese encehalitis virus	Encephalitis	10 [Update number of high-risk countries]	5 (7%)		90%	Under evaluation	10,000/year(ages 0-14)	Campbell, Hills et al. 2011
Oral Cholera (OCV)	Killed, whole cell *Vibro cholerae*	Cholera	N/A	N/A	2 doses age ≥1 year	67-80%	Effectiveness shown for 6 months to 2 years post-vaccination	45,000	Ali et al. 2012; Sack 2014

*Note that the 2008 and 2010 estimates used different methodologies and overall diarrhea mortality envelopes.

Table _.2 Impact of Vaccination in Terms of Children Immunized and Deaths Averted in 73 GAVI-Supported Countries

	Estimates for 2000-2012			Projections for 2013-2020		
	Children immunized	Future deaths averted	Deaths averted per thousand vaccinated	Children immunized	Future deaths averted	Deaths averted per thousand vaccinated
HepB	372,000,000	3,200,000	8.5	470,000,000	3,800,000	8.1
Hib	160,000,000	800,000	5.0	435,000,000	1,900,000	4.4
JE (campaign)	-	-	-	91,000,000	21,000	0.2
JE (routine)	-	-	-	147,000,000	43,000	0.3
Measles (routine 2nd dose)	27,000,000	24,000	0.9	195,000,000	225,000	1.2
Measles (campaign)	--	--	--	660,000,000	1,000,000	1.5
Men A (campaign)	107,000,000	111,000	1.0	149,000,000	155,000	1.0
Men A (routine)	--	--	--	40,000,000	3,000	0.1
Pneumo	11,000,000	86,000	7.9	280,000,000	1,800,000	6.5
Rotavirus	4,000,000	7,000	1.7	280,000,000	480,000	1.7
Rubella (campaign)	--	--	--	506,000,000	345,000	0.7
Rubella (routine)	--	--	--	140,000,000	64,000	0.5
Yellow fever	92,000,000	18,000	0.2	150,000,000	30,000	0.2
HPV	37,000	400	10.9	36,000,000	575,000	15.8

Source: Based on Strategic Demand Forecast Version 7 (Lee, Franzel 2013)

Notes: *Estimated cohort of surviving infants in GAVI eligible countries in 2012 is approximately 75 million. GAVI = Global Alliance for Vaccines and Immunizations

Table _.3 Approximate Range of Cost-Effectiveness Of Various Childhood Vaccines in LICs and LMICs, Various Contexts (US$, 2012 per DALY).

< US$100/DALY	**US$100-$1036 per DALY[a]**	**More than US$1,036/DALY**
Original EPI-6 (BCG, DPT, measles, polio Hepatitis B, where endemic Pneumoccocus, at subsidized GAVI price in LICs and LMICs with high mortality Rotavirus, at subsidized GAVI price in LICs and LMICs with high mortality	Haemophilus influenzae B Yellow fever, at GAVI price, where endemic Japanese encephalitis, at GAVI price Pneumococcus, unsubsidized GAVI price, in LICs and LMICs with high and medium child mortality Rotavirus, unsubsidized GAVI price, in LICS and LMICs with high and medium child mortality Meningitis A	Cholera Typhoid Pneumococcus, discounted price but more than GAVI price, in low child mortality countries Rotavirus, discounted price but more than GAVI price, in low child mortality countries

Notes:
For details of sources and references, see RMNCH volume cost-effectiveness chapter 17.
[a] Low-income countries = per capita GNI in 2012 less than US$1,036; LMICs = per capita GNI from US$1,036-US$4,125 (World Bank 2014).

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Annex A: Supplemental material. Methodologies used for impact of EPI vaccines and new GAVI-supported vaccines (see annex table 2)

Measles: Using a dynamic population-based Markov model developed by Pennsylvania State University and WHO (Chen, Fricks et al. 2012; Simons, Ferrari et al. 2012).

Hep B: Because disease develops over many years, impact of vaccination programs are modeled over the lifetime of birth cohorts. Numbers of expected hepatitis B deaths averted were estimated using a static cohort model based on the natural history of hepatitis B disease developed by the US Centers for Disease Control and Prevention (Goldstein, Zhou, et al 2005). Underlying rates of hepatitis B infection in the model were based on pre-vaccination seroprevalence studies (Goldstein,Zhou, et al 2005).

Hib: Estimates of deaths averted by Hib vaccination were calculated using the Lives Saved Tool (LiST) developed by Johns Hopkins University (Winfrey, McKinnon et al. 2011) [3]. Consistent with the approach used to estimate global Hib pneumonia disease burden (Watt, Wolfson et al. 2009; Theodoratou, Johnson et al. 2010) estimates of the proportion of under-five pneumonia deaths due to Hib pneumonia were derived by applying the proportionate reduction in radiologically confirmed pneumonia cases observed in Hib vaccine probe studies to WHO/CHERG country-specific estimates of the proportion of under-five deaths due to pneumonia in 2000 (Bryce, Boschi-Pinto et al. 2005; Liu, Johnson et al. 2012).

Pneumococcus: Estimates of deaths averted by pneumococcal vaccination were calculated using the LiST tool developed by Johns Hopkins University (Winfrey, McKinnon et al. 2011). The same approach was used to estimate pneumonia deaths due to pneumococcus as described above for pneumonia deaths due to Hib.

Rotavirus: Estimates of deaths averted by rotavirus vaccination were calculated using the LiST tool developed by Johns Hopkins University (Winfrey, McKinnon et al. 2011). To estimate the number of deaths caused by rotavirus, WHO country-specific estimates of under-five deaths due to diarrhea were multiplied by an estimated 39 percent of cases of severe clinical gastroenteritis caused by rotavirus based on 41 hospital-based surveillance studies (Parashar, Gibson et al. 2006; Fischer Walker, Munos et al. 2013). In 2008, it was estimated that 453,000 deaths occurred due to rotavirus worldwide (Tate, Burton et al. 2012), although a more recent estimate using a different methodology and diarrhea mortality envelope estimated 193,000 rotavirus deaths in 2010 (Walker, Rudan et al. 2013).

Rubella: Estimates of CRS disease burden are based on surveillance data, serologic surveys of childbearing-aged women and mathematical modeling. Review of worldwide data on CRS in developing countries suggested incidence of 0.6 to 2.2 cases per 1000 live births, similar to rates seen in developing countries before universal vaccination (Reef and Plotkin, 2013). Estimates of the number of CRS cases averted by vaccination were calculated using a dynamic transmission model developed in 2011 by the UK Health Protection Agency and extended from previous modeling work (Cutts and Vynnycky 1999; Vynnycky, Gay et al. 2003). This model projects the number of women of childbearing age susceptible to rubella infection by country and year through the lifetime of each vaccinated cohort. Estimates of CRS deaths averted were calculated assuming a proportional case fatality ratio of 30 percent in all countries (De Owens and De Espino 1989; Lawn, Reef et al. 2000; Al-Awaidy, Griffiths et al. 2006; Lanzieri, Pinto et al. 2007).

Meningococcus: To calculate these figures, estimates of 1.04 deaths averted per 1,000 persons vaccinated through mass vaccination campaigns and 0.08 deaths averted per 1,000 infants vaccinated through routine vaccination were applied to projected numbers of persons vaccinated. These rates were based on an analysis conducted by PATH using a generalized static cohort model to estimate the impact of a WHO and UNICEF investment case (LaForce and Okwo-Bele 2011). Underlying *Neisseria meningitidis* serogroup A incidence used in the model was based on a prospective hospital-based surveillance study of meningitis in Niger conducted during 1981–1996 (Campagne, Schuchat et al. 1999). The model assumed a ten-year inter-epidemic interval and a 12 percent case fatality ratio.

Yellow fever: An estimate of 0.2 epidemic yellow fever deaths averted per 1,000 persons vaccinated, derived from a 1993 study that modeled the impact of routine infant yellow fever vaccination in Nigeria (Monath and Nasidi 1993), was applied to projected numbers of persons vaccinated to estimate deaths averted during 2000–2020. The reference study utilized a static cohort model based on the assumption that, on average, epidemics occur at 17-year intervals, 4 million persons are affected in each epidemic, there is an epidemic infection rate of 20%, and 20 percent case fatality ratio.

JE: Estimates of Japanese encephalitis deaths averted were calculated using a static cohort model developed by PATH, modified from models developed for Cambodia and India (Suraratdecha, Jacobson et al. 2006; Touch, Suraratdecha et al. 2010). Underlying incidence rates used in the model estimates were based on a recent review of population-based surveillance studies (Campbell, Hills et al. 2011). Country-specific proportional case fatality ratios were based on a review of published and unpublished surveillance data and ranged from 10 to 25 percent (Sohn 2000; Solomon, Dung et al. 2000; Kari, Liu et al. 2006).

For the new vaccines, we used a methodology recently adopted through an expert process with leading modeling groups co-convened by The GAVI Alliance and Bill and Melinda Gates Foundation to estimate impact of vaccinations administered in the 73 GAVI-supported countries (Table 1). The methods and results from the first round of modeling were published (Lee, Franzel et al. 2013), covering vaccinations forecasted to be administered in GAVI supported countries from 2011-2020. Numbers of deaths averted were calculated as the difference in deaths expected to occur over the lifetime of vaccinated cohorts compared to the number of deaths expected to occur in those cohorts without vaccination. We provide an update of this analysis covering vaccinations administered from 2000-2012 and updated forecasts of vaccinations expected to occur between 2013 and 2020 based on the GAVI Alliance Strategic Demand Forecast version 7. Similar evidence on the projected impact of new vaccines in non-GAVI eligible countries would also be valuable to decision-makers in those countries and globally, but at present no systematic and standardized demand forecast exists that projects vaccination uptake and use in such countries.

Annex Table 1. 73 GAVI-Supported Countries and Vaccine Introduction Status, 2012

	Region	Hep B	Hib	PCV	Men A	JE	YF	MSD	Rubella	Rotavirus
Afghanistan	EMRO	X	X					X		
Angola	AFRO	X	X				X			
Armenia	EURO	X	X					X		X
Azerbaijan	EURO	X	X					X		
Bangladesh	SEARO	X	X					X		
Benin	AFRO	X	X	X	X		X			
Bhutan	SEARO	X	X					X	X	
Bolivia	AMRO	X	X				X		X	X
Burkina Faso	AFRO	X	X		X		X			
Burundi	AFRO	X	X	X						
Cambodia	WPRO	X	X					X		
Cameroon	AFRO	X	X	X	X		X			
Central African Republic	AFRO	X	X	X			X			
Chad	AFRO	X	X		X		X			
Comoros	AFRO	X	X							
Congo, Democratic Republic	AFRO	X	X	X			X			
Congo, Republic	AFRO	X	X	X			X			
Côte d'Ivoire	AFRO	X	X				X			
Cuba	AMRO	X	X					X	X	
Djibouti	EMRO	X	X	X				X		
Eritrea	AFRO	X	X							
Ethiopia	AFRO	X	X	X						
Gambia	AFRO	X	X	X			X	X		
Georgia	EURO	X	X					X	X	
Ghana	AFRO	X	X	X	X		X	X		X
Guinea	AFRO	X	X				X			
Guinea-Bissau	AFRO	X	X				X			
Guyana	AMRO	X	X	X			X	X	X	X
Haiti	AMRO	X	X						X	
Honduras	AMRO	X	X	X					X	X
India	SEARO	X	X			X		X		
Indonesia	SEARO	X						X		
Kenya	AFRO	X	X	X			X			
Kiribati	WPRO	X	X					X	X	
Korea, Dem. People's Republic	SEARO	X	X					X		
Kyrgyzstan	EURO	X	X					X	X	
Lao People's Democratic Republic	WPRO	X	X					X	X	
Lesotho	AFRO	X	X							
Liberia	AFRO	X	X				X			

Madagascar	AFRO	X	X	X						
Malawi	AFRO	X	X	X						X
Mali	AFRO	X	X	X	X		X			
Mauritania	AFRO	X	X							
Moldova	EURO	X	X					X	X	X
Mongolia	WPRO	X	X					X	X	
Mozambique	AFRO	X	X							
Myanmar	SEARO	X	X					X		
Nepal	SEARO	X	X			X				
Nicaragua	AMRO	X	X	X				X	X	X
Niger	AFRO	X	X		X		X			
Nigeria	AFRO	X	X		X		X			
Pakistan	EMRO	X	X	X				X		
Papua New Guinea	WPRO	X	X					X		
Rwanda	AFRO	X	X	X						X
Sao Tome and Principe	AFRO	X	X	X			X			
Senegal	AFRO	X	X		X		X			
Sierra Leone	AFRO	X	X	X			X			
Solomon Islands	WPRO	X	X					X	X	
Somalia	EMRO									
Sri Lanka	SEARO	X	X			X		X	X	
Sudan	EMRO	X	X		X			X		X
South Sudan	EMRO									
Tajikistan	EURO	X	X					X	X	
Tanzania	AFRO	X	X	X						X
Timor-Leste	SEARO	X	X							
Togo	AFRO	X	X				X			
Uganda	AFRO	X	X							
Ukraine	EURO	X	X					X	X	
Uzbekistan	EURO	X	X					X	X	
Vietnam	WPRO	X	X			X		X		
Yemen	EMRO	X	X	X				X		X
Zambia	AFRO	X	X							
Zimbabwe	AFRO	X	X	X						
Total Countries		**73**	**70**	**24**	**10**	**4**	**24**	**32**	**18**	**12**

Source:

Note: HepB = Hepatitis B; Hib = Haemophilus influenza type b; JE = Japanese encephalitis; PCV = pneumococcal conjugate vaccine; MenA = Meningococcus serotype A; MSD = measles second dose; Rota = rotavirus; YF = Yellow Fever.

Annex Table 2. Models used to estimate averted cases and deaths from administration of original EPI vaccines and new and underutilized vaccines supported by GAVI				
Vaccines	Vaccination strategies	Model source	Model structure	Underlying disease burden
BCG	routine	Trunz et al, 2006		
DTP	routine			
Polio	routine and campaign			
Measles	routine and campaign	Chen, Fricks et al. 2012; Simons, Ferrari et al. 2012 (Pennsylvania State University and WHO)	Dynamic population-based Markov model informed by surveillance data	Case-fatality ratios for children <5 years and 5-9 years applied to age distribution derived from case-based surveillance data, using first dose coverage and region as covariates
Hepatitis B	routine	Goldstein et al, 2005 (U.S. Centers for Disease Control and Prevention)	Static natural history population-based cohort	Pre-vaccination hepatitis B surface antigen (HBsAg) serosurvey data
Haemophilus influenzae type b (Hib)	routine	Lives Saved Tool model (Johns Hopkins University)	Static cohort	Pneumonia deaths <5 years (WHO) x Hib vaccine preventable burden of radiographic pneumonia
Pneumococcal	routine	Lives Saved Tool model (Johns Hopkins University)	Static cohort	Pneumonia deaths <5 years (WHO) x pneumococcal conjugate vaccine preventable burden of radiographic pneumonia
Rotavirus	routine	Lives Saved Tool model (Johns Hopkins University)	Static cohort	Diarrhea deaths <5 years (WHO) x proportion of severe gastroenteritis due to rotavirus infection
Rubella	campaign & routine	UK Health Protection Agency Centre for Infections, CDC, WHO	Dynamic cohort	Pre-vaccination rubella serosurveys to determine age-specific incidence

Meningococcal serogroup A	campaign & routine	Long Range Cost and Impact model (GAVI)	Deaths averted per 1,000 vaccinated	Pre-vaccination prospective hospital surveillance study in Niger, 1981-1996
Yellow fever	routine	Long Range Cost and Impact model (GAVI)	Deaths averted per 1,000 vaccinated	Model based on disease burden studies in Nigeria
Japanese encephalitis	campaign & routine	PATH	Static cohort	Population based surveillance studies