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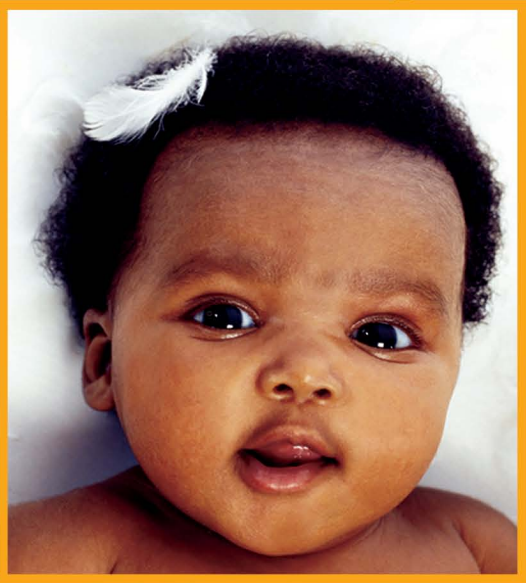

Control of Diphtheria, Pertussis, Tetanus, *Haemophilus influenzae* type b and Hepatitis B Field Guide

Pan American Health Organization
Regional Office of the World Health Organization

Control of Diphtheria, Pertussis, Tetanus, *Haemophilus influenzae* type b, and Hepatitis B

Field Guide

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ABOUT THE IMMUNIZATION FIELD GUIDES

The Expanded Program on Immunization is viewed as one of the most successful public health experiences in the Americas because it has played a pivotal role in reducing infant mortality from vaccine-preventable diseases in the Region. In fact, since the program was launched, our countries stopped the transmission of wild poliovirus in the Region in 1991 and interrupted indigenous measles transmission in November 2002; they also are making significant gains in the battle to eliminate rubella and congenital rubella syndrome. In addition, national immunization programs are undertaking extraordinary efforts to identify at-risk populations and overcome inequities in vaccination. To maintain these advances and to cope with new challenges, such as the introduction of new vaccines, partnerships will have to be strengthened among governments, donor agencies, the private sector, scientific associations, and society as a whole.

To this end, PAHO is promoting the best technical quality by issuing these practical field guides that have been prepared by the Immunization Unit in the Family and Community Health Area. The most recent techniques presented in the field guides, coupled with useful illustrations, will help health workers in their efforts to control, eliminate, or eradicate diseases such as poliomyelitis, neonatal tetanus, yellow fever, diphtheria, pertussis, tetanus, *Haemophilus influenzae* type b infections, hepatitis B, measles, and rubella. The field guides also include standardized methods and procedures for conducting epidemiological surveillance and maintaining an up-to-date information system that makes it possible to take timely and effective decisions.

These field guides are based on the latest scientific information and they bring together the experience of prominent health professionals in the field. As a result, they are particularly suitable for promoting strategies that have already proven to be effective. The strengthening of prevention activities, the reduction of health inequities, and the promotion of technical expertise in vaccination services were the principles that guided the preparation of the guides.

The Expanded Program on Immunization, a joint effort of all the countries of the Americas, effectively contributes to the attainment of the Millennium Development Goals.

Dr. Mirta Roses Periago
Director
Pan American Health Organization

PREFACE

This Field Guide is a tool to facilitate the work of health officials and field staff involved in national immunization programs. Given the widespread use of a combination vaccine against diphtheria, pertussis, tetanus, *Haemophilus influenzae* type b (Hib), and hepatitis B (referred to here as pentavalent vaccine) in the Americas, this guide addresses all five diseases prevented by this vaccine. A separate guide on neonatal tetanus is available, as this condition is targeted for elimination, and specific vaccination and surveillance strategies apply.

The guide summarizes clinical information on the five diseases, outlines the strategies to control and prevent them, and examines existing vaccines, including some combination vaccines. Combination vaccines support the achievement of one of the Pan American Health Organization's (PAHO) priority initiatives—the introduction of "new" vaccines into national immunization programs—and their use is likely to become widespread in the Americas.

As an additional feature, this guide provides the codes of the International Classification of Diseases, revisions 9 and 10 (ICD-9 and ICD-10), for each disease to facilitate the active search of cases in hospital records and other sources of data using the ICD classification.

The information included in this manual was compiled from several textbooks, PAHO and World Health Organization (WHO) recommendations and position papers, and other PAHO materials, such as training modules and technical documents. Some of the surveillance tools presented here may have to be adapted locally to accommodate rapid implementation of control activities and resulting changes in the local epidemiology of these diseases.

PAHO recognizes the achievements of the health workers of the Region of the Americas in eliminating and controlling vaccine-preventable diseases. PAHO also anticipates that the experience of its Member States in controlling the diseases addressed in this guide, and their success in spearheading the introduction of "new" vaccines such as those against Hib and hepatitis B into national immunization programs, can in the future be shared with other regions of the world.

GLOSSARY

Administrative coverage The most common method to calculate coverage rates. It is calculated by dividing the number of doses administered as reported using the registry system (only doses given during routine immunization services) by the target population, for example, children aged < 1 year of age, and it is expressed as a percentage.

$$\text{Administrative coverage} = \frac{\text{Number of vaccine doses administered}}{\text{Target population}} \times 100$$

Attack rates The proportion of people in a population who develop a disease within a specific time interval, usually in the context of an outbreak. It is the number of new cases of a disease divided by the population at risk, for example, children attending a school where cases have been identified, and it is often expressed as a percentage. Attack rates can be calculated for a specific geographical area, a specific age group, or by vaccination status.

$$\text{Attack rate} = \frac{\text{Number of new cases}}{\text{Population at risk}} \times 100$$

Case fatality rate The number of deaths from a specific cause divided by the number of cases of that disease expressed as a percentage.

$$\text{Case fatality rate} = \frac{\text{Number of deaths}}{\text{Number of cases}} \times 100$$

Combination (multivalent) vaccine A vaccine made by combining two or more vaccines; for example, diphtheria-pertussis-tetanus (DPT) is a combination vaccine.

Conjugate vaccine A vaccine made by chemically joining two different substances. In the case of *Haemophilus influenzae* type b (Hib) vaccines, an Hib polysaccharide is joined with a protein carrier.

Dropout rate

The percentage of children who receive a first dose of vaccine but do not complete the minimum vaccination schedule of three doses of DPT or OPV, which are necessary to provide full protection. This rate is usually expressed as a percentage. The drop-out rate is used as an indicator of performance of the immunization systems.

$$\text{Dropout}^{\dagger} = \frac{\text{No. of children receiving 1 dose} - \text{No. of children receiving 3 doses}}{\text{No. of children receiving 1 dose}} \times 100$$

Formulation

The form in which a vaccine is presented, for example, liquid or lyophilized (freeze-dried), single or in combination.

Gram's stain

Gram's stain is a method for staining samples of bacteria that differentiates between the two main types of bacterial cell wall. Bacteria can be classified as Gram-positive or Gram-negative according to the color resulting from the Gram's stain.

Incidence

The probability of developing a disease or condition over a given period of time, usually one year. It is calculated as the proportion of people in a population at risk who develop a disease within the specified time interval and it is usually expressed per 1,000, per 10,000, or per 100,000 individuals. It can be calculated for a specific geographical area, a specific age group, or by vaccination status.

$$\text{Incidence proportion} = \frac{\text{Number of new cases}}{\text{Population}} \quad \text{per 1,000; or 10,000; or 100,000}$$

Lyophilized

Freeze-dried or dried in a frozen state under high vacuum for preservation. For example, some Hib vaccines are lyophilized.

†A negative calculation is usually indicative of problems with the registration of vaccine doses.

Monovalent vaccine A vaccine containing antigen to induce protection against a single microorganism.

Pentavalent vaccine A combination vaccine containing antigens to induce protection against five microorganisms. In this guide pentavalent vaccine refers to diphtheria-tetanus-pertussis-*Haemophilus influenzae* type b-hepatitis B vaccine.

ACRONYMS

aP	acellular pertussis vaccine
CDC	Centers for Disease Control and Prevention (United States)
CSF	cerebrospinal fluid
DFA	direct fluorescent antibody test
DPT	diphtheria-pertussis-tetanus vaccine (whole cell pertussis, wP)
DT	diphtheria-tetanus vaccine for children
DTaP	diphtheria-tetanus-acellular pertussis vaccine
HBIG	hepatitis B immune globulin
HbOC	*Haemophilus influenzae* type b oligosaccharide conjugate vaccine
Hep B	hepatitis B vaccine
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
ICD-9	International Classification of Diseases, 9th Revision
ICD-10	International Classification of Diseases, 10th Revision
IM	intramuscularly (by intramuscular injection)
IPV	inactivated polio vaccine (injectable)
IV	intravenously (by intravenous injection)
PAHO	Pan American Health Organization
PCR	polymerase chain reaction
PRP	polyribosylribitol phosphate (a polysaccharide of the external capsule of Hib)
Td	tetanus-diphtheria vaccine for persons over 7 years of age
TIG	tetanus immune globulin
TT	tetanus toxoid
WHO	World Health Organization
wP	whole cell pertussis vaccine

1 DIPHTHERIA

[ICD-9 032; ICD-10 A36]

1.1 INTRODUCTION

Diphtheria is an acute bacterial disease that can cause infection of the nasopharynx, which can result in obstruction of the airway and, eventually, death. Additionally, the toxin produced by the bacteria can result in systemic complications of various organs. The use of antitoxin, improvements in treatment, and widespread immunization using the toxoid have dramatically reduced mortality and morbidity due to diphtheria. Nevertheless, vaccination continues to be essential to prevent the disease and to avoid large epidemics, such as those occurring in countries where there has been an accumulation of susceptible individuals (*1*).

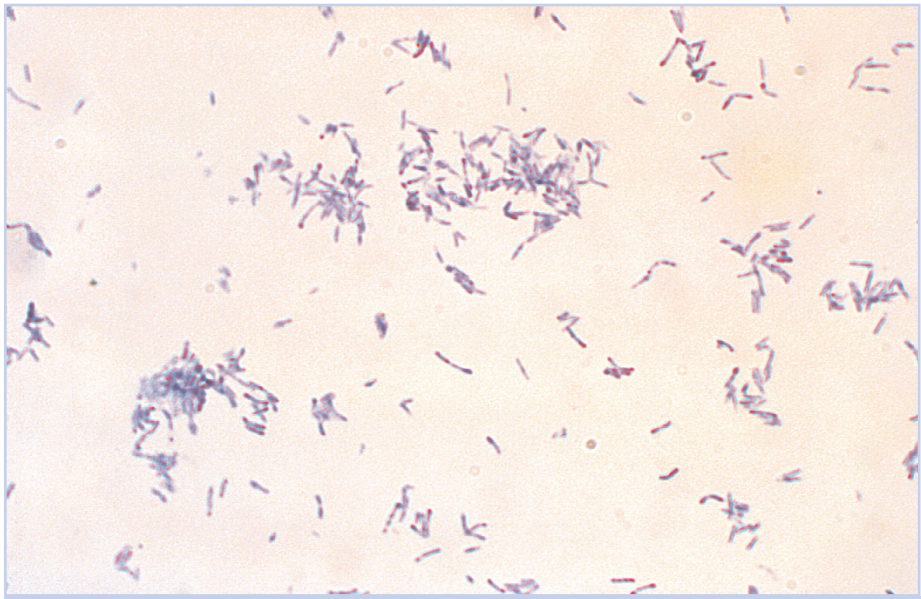
The following five activities are crucial for diphtheria control:

- Adequate surveillance;
- High levels of routine immunization in appropriate age groups;
- Prompt recognition of the disease and appropriate case management, including the maintenance of adequate supplies of antitoxin and antibiotics;
- Rapid case investigation and management of close contacts;
- Outbreak management.

1.2 EPIDEMIOLOGY[a]

1.2.1 Infectious Agent

Diphtheria is caused by the exotoxin produced by toxigenic strains of the Gram-positive bacterium *Corynebacterium diphtheriae* (Figure 1). Four biotypes exist: *mitis*, *intermedius*, *gravis*, and *belfantis*. For the bacteria to produce this exotoxin, it must be infected by a virus—the corynebacteriophage—contain-



Credits: Centers for Disease Control and Prevention

Figure 1. Photomicrograph of *Corynebacterium diphtheriae* (magnified 1200x).

[a]See Annex 1, "Summary of the epidemiological characteristics of diphtheria, pertussis, tetanus, *Haemophilus influenzae* type b (Hib), and hepatitis B."

ing the gene *tox*. Nontoxigenic strains of *C. diphtheriae* rarely cause disease and, when they do, the disease is usually mild and with no systemic complications. Nontoxigenic strains, however, can cause cutaneous diphtheria and have been associated with cases of endocarditis.

1.2.2 Occurrence

Diphtheria was one of the most common causes of morbidity and mortality among children in the pre-vaccine era. Death rates declined with the availability and use of the diphtheria antitoxin and, presumably, other therapeutic measures such as intubation. The incidence of the disease has declined dramatically worldwide with the introduction of active immunization with diphtheria toxoid. However, diphtheria remains endemic in several areas of the world, including some countries of the Caribbean and Latin America (*2*, *3*).

Historically, the disease peaks about every 10 years and outbreaks occur. Most diphtheria cases occur in colder months in temperate climates and in children aged less than 15 years. However, the majority of cases in recent outbreaks, such as a large outbreak in the Russian Federation in the 1990s and cases reported in the United States since 1980, are among persons aged 15 years and older (*1, 4*). In tropical areas, the seasonality of the disease is less pronounced, and the cases are milder, with more inapparent, cutaneous, and wound diphtheria cases occurring (*1*).

Given that *C. diphtheriae* is ubiquitous and carriers exist worldwide, continuing diphtheria immunization is crucial to keeping this disease under control.

1.2.3 Transmission

C. diphtheriae is transmitted from person to person via the respiratory tract of a case or transient carrier (i.e., a person carrying the bacterium who does not have the disease). Rarely, transmission can occur via contact with skin lesions or fomites (e.g., articles soiled with discharge from lesions of infected people).

1.2.4 Reservoir

Humans are the only natural host for *C. diphtheriae*; carriers of the bacterium are the reservoir.

1.2.5 Incubation

The incubation period is two to five days (with a range of 1 to 10 days) after infection with *C. diphtheriae* (*5*).

1.2.6 Communicability

The period of communicability varies. Transmission can occur as long as the toxigenic bacteria are present in discharge and lesions, which is normally two weeks or less, and seldom longer than four weeks. Antibiotic therapy promptly terminates

shedding of the bacilli. There are rare occasions in which chronic carriers shed the bacilli for six months or more.

1.2.7 Immunity

Even in the pre-vaccine era, diphtheria was rare in infants aged less than 6 months, likely because of the presence of maternal antibodies. Thereafter, most people acquired immunity to diphtheria without experiencing the disease.

After receiving three doses of the toxoid, virtually all infants and adults develop diphtheria antitoxin titers considered to be protective. Immunization provides long-lasting but not lifelong immunity, as measured by antitoxin titers. However, some adults who were immunized at a young age can have immunological memory and would be protected if exposed to diphtheria toxin. The protection provided by the toxoid is against systemic disease but not against colonization of the nasopharynx.

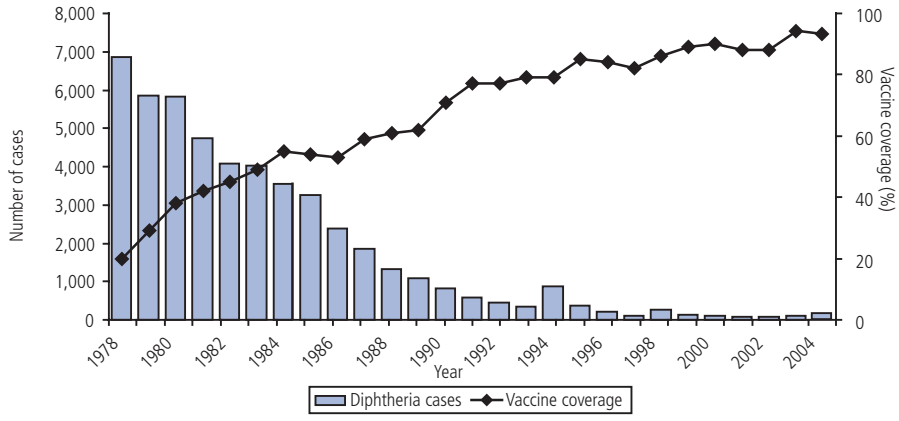
1.2.8 Changing Epidemiology

Before the Expanded Program on Immunization began in 1977, it is estimated that close to 1 million cases of diphtheria and 50,000–60,000 deaths due to the disease and its complications occurred globally each year. In 2002, only 9,235 cases of diphtheria were reported worldwide.[b] This trend has also been seen in the Region of the Americas (Figure 2).

Despite the marked decline in incidence since the widespread use of the toxoid, large outbreaks have occurred, most notably in the 1990s in the countries of the former Soviet Union. This outbreak started in the Russian Federation in 1990, and spread to the Newly Independent States and to Mongolia. Over 150,000 cases and 5,000 deaths were reported between 1990 and 1997. In this outbreak, more cases occurred in young adults than in children (*1*).

In the Region of the Americas between 1993 and 2004, outbreaks were reported in Colombia, the Dominican Republic, Ecuador, Haiti, and Paraguay (Table 1). The outbreak in Ecuador, which occurred in 1993–1994, was the

Figure 2. Number of diphtheria cases notified and DPT3 vaccine coverage among children aged less than 1 year, Region of the Americas, 1978–2004.



Source: Pan American Health Organization, Family and Community Health Area, Immunization Unit.

[b]Data from the World Health Organization (www.who.int).

Table 1. Characteristics of three recent diphtheria outbreaks in Latin America[a]

	Ecuador	Colombia	Paraguay
Year	1993–1994	2000	2002
Number of cases	724	12	50[b]
Case-fatality rate	N/A	12%	15%
Vaccination coverage	Low coverage	Decreased coverage	Low coverage
Performance of the surveillance system	Improved response in the 1994 outbreak	Adequate	Problems notifying cases and delays in implementing control measures
Vaccination status of the cases	15% unvaccinated; 22% received some doses (no documentation); no information available for balance of cases	62% incomplete vaccination	74% without vaccination history
Most affected age group	86% among those ≥15 years of age	50% among those 5–9 years of age	57% among those 5–14 years of age
Socioeconomic status/living environment	Low; urban slums	Low; urban slums	Low; urban slums
Control measures taken	Vaccination for children <5 years of age; booster dose; vaccination of adults at risk	Vaccination for children <5 years; booster dose; vaccination of adults at risk	Vaccination for children <5 years; booster dose; vaccination of adults at risk

[a] Data obtained from country reports submitted to PAHO.
[b] Last figure published as of week 40, 2002.

Source: Ropero AM, Oliva O, Castillo-Solorzano C, Dietz V, Izurieta H, Carrasco P, et al. Recent outbreaks of diphtheria in the Americas. Abstract presented at the XV Technical Advisory Group (TAG) Meeting on Vaccine-preventable Diseases, Pan American Health Organization, 22–23 November, Washington, D.C., 2002.

largest, with over 500 cases reported. Most cases in these outbreaks occurred in overcrowded and poor areas, and among people with incomplete vaccination or no vaccination history. A shift in the age distribution toward older ages was observed in the outbreak in Ecuador, where half of the cases were among persons aged 15 years or older (*6, 7*).

1.3 CLINICAL ASPECTS

1.3.1 Pathogenesis

The exotoxin is the main pathogenic factor in the development of diphtheria. As mentioned earlier, only *C. diphtheriae* infected by a bacteriophage containing the gene *tox* produces the toxin. The toxin produced at the site of the diptheritic mem-

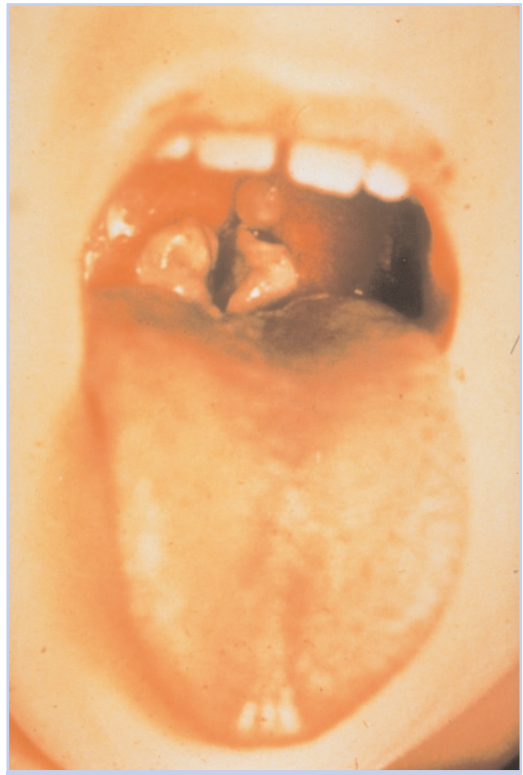
brane is adsorbed into the bloodstream and is responsible for remote manifestations of diphtheria, such as myocarditis, nephritis, and neuritis.

1.3.2 Clinical Features

Diphtheria usually involves the respiratory tract, but can affect any mucosal membrane. The disease has an insidious onset, with nonspecific mild symptoms and signs; fever is usually low and rarely exceeds 38.5°C. Symptoms and signs are proportional to the amount of toxin. If enough toxin is adsorbed, the patient can appear pale, have a rapid pulse, and become severely prostrated.

Diphtheria can be classified according to the site of infection:

- *Nasal diphtheria*: This form is characterized by a mucopurulent nasal discharge, which can become blood-tinged, and a white membrane that can form in the nasal septum. Isolated nasal diphtheria is uncommon and usually mild; its diagnosis can easily be missed.
- *Pharyngeal and tonsillar diphtheria*: This constitutes the "classic" form and concomitant involvement of other sites—respiratory or not—can occur. At first, the pharynx can be injected at examination, but soon, small white patches appear and grow, forming a grayish-white adhering membrane that can cover the entire pharynx, including the tonsils, uvula, and soft palate (see Figure 3). Attempts to dislodge the membrane cause bleeding. Edema and inflammation of the surrounding soft tissues and painful enlargement of the anterior cervical lymph nodes can result in the so-called "bull neck," which is indicative of severe infection. Left untreated, the membrane softens after about a week and gradually sloughs off in pieces or as a single block. Systemic symptoms begin to disappear as the membrane falls off.
- *Laryngeal diphtheria*: This form can occur in isolation (the pharyngeal lesion may not develop) or can be an extension of the pharyngeal form. It is more common in children aged less than 4 years, and presents as gradually progressing hoarseness, barking cough, and stridor. It can lead to pharyngeal obstruction and death.
- *Cutaneous (skin) diphtheria*: This is a mild skin infection that can be caused by toxin-producing or non–toxin-producing bacilli, whereas all other forms of diphtheria are caused by toxin-producing organisms. It is more common in the tropics, and has often been associated with poverty and overcrowding. Individuals with cutaneous diphtheria can serve as the source of infection for others.



Credit: Centers for Disease Control and Prevention, United States.

Figure 3. Diphtheria membranes.

LABORATORY TESTS FOR DIPHTHERIA

Bacteriological culture:
• Is essential to confirm diphtheria diagnosis;
• Should be collected before starting antibiotic therapy;
• Needs tellurite-containing media;
• Can be used for detecting *C. diphtheriae* among contacts.
Toxigenicity tests:
• Is used to determine toxin production in the isolated *C. diphtheriae.*
Polymerase chain reaction (PCR):
• Is useful for detecting diphtheria toxin gene;
• Can be used even after antibiotics have been started;
• Is available only in selected reference laboratories;
• Does not replace culture for confirming diphtheria diagnosis.

1.3.3 Laboratory Diagnosis

The best samples for bacteriological culture are pharyngeal swabs obtained under direct visualization, preferably from the edge of or directly beneath the membrane. In general, Gram's stains are not recommended as other *Corynebacterium* species can normally inhabit the throat. After *C. diphtheriae* has been isolated, the biotype can be determined.

To ascertain if the isolated *C. diphtheriae* is toxigenic, testing for toxin production is usually available only in selected reference laboratories.

1.3.4 Differential Diagnosis

The differential diagnosis of diphtheria includes:

- Bacterial (especially streptococcal) and viral pharyngitis;
- Vincent's angina (caused by anaerobic organisms);
- Infectious mononucleosis;
- Oral syphilis;
- Candidiasis.

For laryngeal diphtheria, the differential diagnosis includes epiglottitis caused by:

- *Haemophilus influenzae* type b;
- Spasmodic croup;
- The presence of a foreign body;
- Viral laryngotracheitis.

1.3.5 Complications

The severity of the signs and symptoms is usually proportional to the extent of the local inflammation, which is related to the production of the toxin in the diphtheritic membrane. Severe complications include respiratory obstruction, acute systemic toxicity, myocarditis, and neurological complications (usually neuritis) (*1*).

Local complications are related to the extension of the membrane:

- Laryngeal diphtheria and aspiration of the membrane (or part of it) can lead to respiratory obstruction;
- If the membrane extends downward, it can result in pneumonia and respiratory obstruction;
- Sinusitis and otitis media are usually associated with nasopharyngeal diphtheria due to edema of the upper respiratory tract.

Systemic complications resulting from diphtheria toxin include:

- Myocarditis is the main cause of diphtheria-related mortality. It can be complicated by heart blocks and can progress to congestive heart failure. Early myocarditis occurs between the third and seventh day of infection and is usually fatal. Less severe, late myocarditis usually occurs the second week after onset and, occasionally, later.
- Neurological complications mostly manifest as a toxic peripheral neuropathy that primarily affects the motor nerves. These complications usually begin two to eight weeks weeks after the onset of illness. Paralysis of eye muscles, limbs, and diaphragm can occur after the fifth week. Diaphragmatic paralysis can be serious, causing pneumonia or requiring mechanical ventilation. Normally, these neurological complications resolve completely.

The case-fatality rate for noncutaneous diphtheria is 5% to 10%, and has remained at those levels for the last 50 years. Children aged less than 5 years and persons over 40 years have a higher risk of death (*1, 5*).

1.3.6 Treatment

Prompt recognition and treatment of diphtheria are very important, as the early use of diphtheria antitoxin is associated with a better outcome. Complications are directly proportional to the number of days between the onset of illness and administration of antitoxin. The patient should be isolated (strict isolation for pharyngeal diphtheria, and contact isolation for cutaneous diphtheria). Treatment should be started immediately after taking bacteriological specimens, without waiting for laboratory confirmation.

Antitoxin. The use of diphtheria antitoxin[c] is the centerpiece of diphtheria treatment, and it should be administered when diphtheria is suspected. Antitoxin will neutralize circulating (unbound) toxin, but not toxin already fixed to the tissues. For this reason, the entire therapeutic dose should be administered at one time. The antitoxin can be given intramuscularly (IM) or intravenously (IV); therapeutic levels of antitoxin in the blood can be achieved faster with IV administration, and this method is usually preferred. The dose to be used ranges from 20,000 to 120,000 units, depending on the size of the lesions, as the amount of toxin produced depends on the size of the membranes and the interval since the time of onset (see Table 2). Since the antitoxin is produced in horses, some experts suggest testing for hypersensitivity to equine serum (*8, 9*).

Table 2. Suggested dose ranges for the use of diphtheria antitoxin

Dose (units)	Indication
20,000 to 40,000	Pharyngeal or laryngeal disease of 48 hours' duration or less Cutaneous disease*
40,000 to 60,000	Nasopharyngeal lesions
80,000 to 120,000	Extensive disease of three or more days' duration or diffuse swelling of the neck

* No consensus exists regarding the value of using antitoxin for cutaneous diphtheria.

Source: American Academy of Pediatrics. Diphtheria. *In:* Pickering LK, ed. *Red book: 2003 report of the Committee on Infectious Diseases*, 26th ed. Elk Grove Village, IL: American Academy of Pediatrics; ©2003:263-266, with permission.

The antitoxin is **not** indicated for prophylaxis.

Antibiotics. Patients with diphtheria should also receive antibiotics to eliminate the bacteria and thus reduce the duration of communicability and carriage. However, **antibiotics are not a substitute for the antitoxin**.

The recommended antibiotics are (*8*):

- Procaine penicillin G. It should be administered intramuscularly, at a dose of 25,000–50,000 units/kg/day for children and 1.2 million units/day for adults, in two divided doses **or**
- Erythromycin. Parenteral erythromycin (40–50 mg/kg/day, with a maximum of 2 g per day) may be used until the patient can swallow, after which he or she may be given erythromycin orally in four divided doses per day or oral penicillin V (125–250 mg four times per day).

Treatment should continue for 14 days.

Other Measures. Nonspecific supportive measures are indicated in addition to antitoxin, isolation, and the use of antibiotics. Additionally, initiation or completion of active immunization against diphtheria is recommended for cases during the convalescent period, because disease does not necessarily confer immunity.

[c]For Latin America and the Caribbean, diphtheria antitoxin can be obtained through the PAHO Revolving Fund for Vaccine Procurement by contacting the Immunization Unit at PAHO Headquarters (Washington, D.C.).

1.3.7 Management of Contacts[d]

- **Vaccination.** The diphtheria vaccination status of case contacts should be assessed to complete the primary three doses of diphtheria vaccine in those who need it, give the fourth dose to children who have received the primary series, and give an age-appropriate diphtheria booster if no booster has been given in the previous five years.
- **Antibiotics.** Prophylactic antibiotics are also indicated for contacts: one dose of benzathine penicillin G, IM (600,000 units for persons aged less than 6 years, and 1.2 million units for those aged 6 or older), or 7 to 10 days of oral erythromycin (40 mg/kg/day for children and 1 g/day for adults). If compliance cannot be guaranteed, one dose of benzathine penicillin is preferred for prophylaxis. If the contact is cultured and the result is positive, he or she should be treated as a case (*8*).

When feasible, management of close contacts also includes keeping them under surveillance for seven days to detect disease, and taking nose and throat samples for culture before starting antibiotic prophylaxis.

TREATMENT OF DIPHTHERIA CASES AND MANAGEMENT OF CONTACTS

Case management includes:
• Administration of antitoxin;
• Antibiotic therapy (after sample collection) with penicillin or erythromycin;
• Isolation of case;
• Supportive measures including vaccination with an age-appropriate diphtheria-containing vaccine.
Contact management includes:
• Vaccination to complete the primary series or use of an age-appropriate diphtheria booster;
• Prophylactic antibiotic treatment with penicillin or erythromycin;
• Close monitoring and follow-up for seven days.

1.4 VACCINATION ACTIVITIES

1.4.1 Routine Immunization

The priority goal for diphtheria control for every country is to reach at least 95% coverage with three primary doses of pentavalent vaccine among 1-year-old children in

[d]A contact is defined as a person of any age living under the same roof as the case; if the patient attends school, his/her classmates are also contacts. In overcrowded areas, contacts may include close neighbors.

each municipality (*10*). High levels of routine immunization coverage in appropriate age groups are crucial to maintaining high immunity levels in the community.

1.4.2 Other Vaccination Activities

Contacts of a diphtheria case should also be vaccinated according to their age and vaccination status (see Management of Contacts in Section 1.3.7). Routine use of tetanus-diphtheria (Td) vaccine, rather than monovalent tetanus toxoid, also helps maintain diphtheria immunity in adults.

1.4.3 Outbreak Control

To control diphtheria outbreaks, defined as the occurrence of a higher number of cases than expected based on previous years, the priority should be intensified diphtheria vaccination through a combined approach of mass vaccination efforts and strengthening of routine services. Vaccination efforts should target affected areas and areas with low coverage levels, covering the largest possible proportion of the population group involved. Health officials should ensure that the population receives adequate diphtheria protection with the three primary doses of the vaccine and boosters in accordance with age. Several vaccination strategies can be employed, such as door-to-door vaccination, fixed vaccination posts, and in-school vaccination.

In some countries of the Americas, the creation of *ad hoc* committees to review diphtheria case data during an outbreak has proven a useful tool for improving case management, case notification, and epidemiological investigation. These committees can be composed of local health authorities, clinicians, epidemiologists, public health nurses, laboratory personnel, and others related to the outbreak. They should meet on a regular basis (daily, weekly, or monthly) to review clinical, epidemiological, and laboratory data, including management of contacts, of each diphtheria case reported.

2 PERTUSSIS (WHOOPING COUGH)

[Pertussis ICD-9 033.0; ICD-10 A37.0]
[Parapertussis ICD-9 033.1; ICD-10 A37.1]

2.1 INTRODUCTION

Pertussis, or whooping cough, is an acute disease of the respiratory tract caused by the Gram-negative bacillus *Bordetella pertussis*. The disease is characterized by a cough that becomes paroxysmal and can last for months. Infants and young children are more severely affected and can suffer paroxysms of cough that end in the characteristic, inspiratory "whoop." Parents of children with pertussis are often devastated by the breathing difficulties their children experience with this life-threatening disease.

Globally, the World Health Organization estimates that 20–40 million cases and 200,000–400,000 deaths occur each year, making pertussis one of the leading causes of vaccine-preventable deaths in the world (*11*, *12*). Vaccination is the main tool for prevention, and high routine vaccination coverage is crucial to controlling this disease.

2.2 EPIDEMIOLOGY[a]

2.2.1 Infectious Agent

Pertussis is caused by the pertussis bacillus *Bordetella pertussis*. *Bordetella parapertussis* causes a similar but usually milder illness, known as parapertussis.

2.2.2 Occurrence

Pertussis occurs worldwide, regardless of climate and latitude. Reported pertussis cases and deaths are more common among females. It is an endemic disease, with peaks every two to five years (most commonly every three to four years). The decrease in incidence has not affected its periodicity, suggesting continued circulation of the infectious agent in the community. Outbreaks occur periodically (*13*, *14*, *15*).

2.2.3 Transmission

B. pertussis is transmitted from person to person via aerosolized droplets produced from a cough or sneeze, or by direct contact with secretions from the respiratory tract of infectious individuals. Pertussis is a highly contagious disease, with secondary attack rates among susceptible household contacts as high as 90%, and 50%–80% in school settings. In several studies, household members have been documented to have been the source of pertussis in infants (*13*, *16*).

[a]See Annex 1, "Summary of the epidemiological characteristics of diphtheria, pertussis, tetanus, *Haemophilus influenzae* type b (Hib), and hepatitis B."

2.2.4 Reservoir

Humans are the only known host for *B. pertussis*. Adolescents and adults are an important reservoir and a source of infection for infants (*14*, *15*).

2.2.5 Incubation

The incubation period is usually seven to ten days (with a range of four to twenty-one days) (*14*).

2.2.6 Communicability

Persons with pertussis are most infectious during the catarrhal period and the first two weeks after cough onset (i.e., approximately 21 days) (*14*). Some individuals, such as infants who remain culture-positive for several weeks, can be infectious for a longer period. Persons not treated with antibiotics are considered contagious for up to three weeks after the onset of typical paroxysms (*16*). In persons treated with erythromycin, infectiousness is reduced to approximately five days after the beginning of the antibiotic therapy (*15*).

2.2.7 Immunity

Maternal protection of infants has not been demonstrated and infants are susceptible to pertussis from the first weeks of life. Pertussis can occur at any age but is most commonly reported, and probably recognized, among children aged less than 5 years. Older individuals infected with pertussis usually present a milder respiratory disease that is often indistinguishable from other causes of cough. Vaccine-induced immunity can wane, explaining the occurrence of cases—mostly seen in industrialized countries—among previously immunized adolescents and adults.

2.2.8 Changing Epidemiology

Pertussis was one of the most common childhood diseases in the pre-vaccine era, and even though its incidence has decreased dramatically since the introduction of pertussis vaccine, it remains a significant public health problem among children in the developing world. Additionally, a rise in pertussis incidence has been seen in countries where anti-immunization movements have led to reductions in vaccination coverage, illustrating the importance of maintaining high vaccination coverage levels for pertussis control.

Recently, heightened recognition of outbreaks and cases among adolescents and adults has led to a better understanding of these persons' role in introducing the pertussis bacillus into households with susceptible young children.

In the Americas, the incidence of pertussis has declined markedly (see Figure 4), but outbreaks still occur. Since the 1990s, an average of about 20,000 cases and 200 deaths have been reported in the Region annually.[b] However, the actual numbers are like-

[b]Data provided by the Immunization Unit, Family and Community Health Area, Pan American Health Organization, Washington, D.C. (*www.paho.org*).

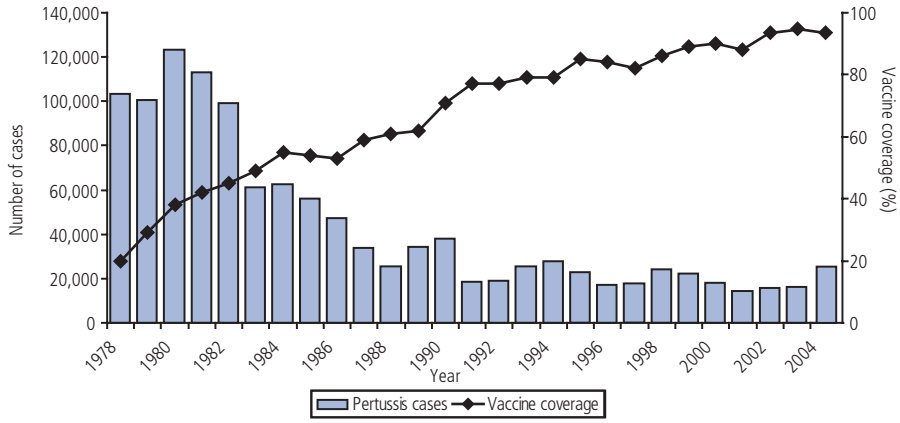
ly to be much higher, since cases may not be diagnosed and under-reporting may be considerable.

2.3 CLINICAL ASPECTS

2.3.1 Pathogenesis

It is believed that *B. pertussis* attaches to ciliated cells in the nasopharynx, where it proliferates and spreads into ciliated cells in the trachea and bronchi, producing toxins that paralyze the cilia and cause cell death. This causes inflammation of the respiratory tract that interferes with normal clearing of pulmonary secretions. Bacteremia does not occur.

Figure 4. Number of pertussis cases notified and DPT3 vaccine coverage among children aged less than 1 year, Region of the Americas, 1978–2004.



Source: Pan American Health Organization, Family and Community Health Area, Immunization Unit.

2.3.2 Clinical Features

Pertussis is characterized by spasms (paroxysms) of severe coughing, which are continuous and without inspiration until the end of the spasm, when there is often a characteristic inspiratory "whoop" and/or post-tussive vomiting (see Figure 5).

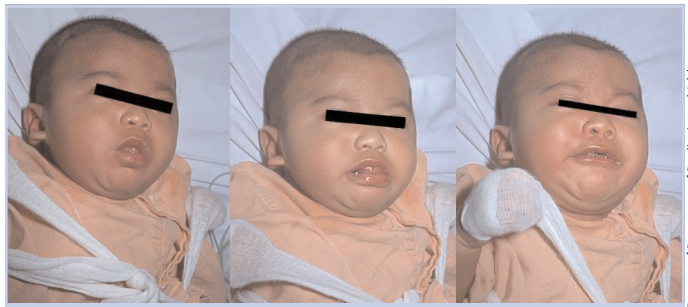


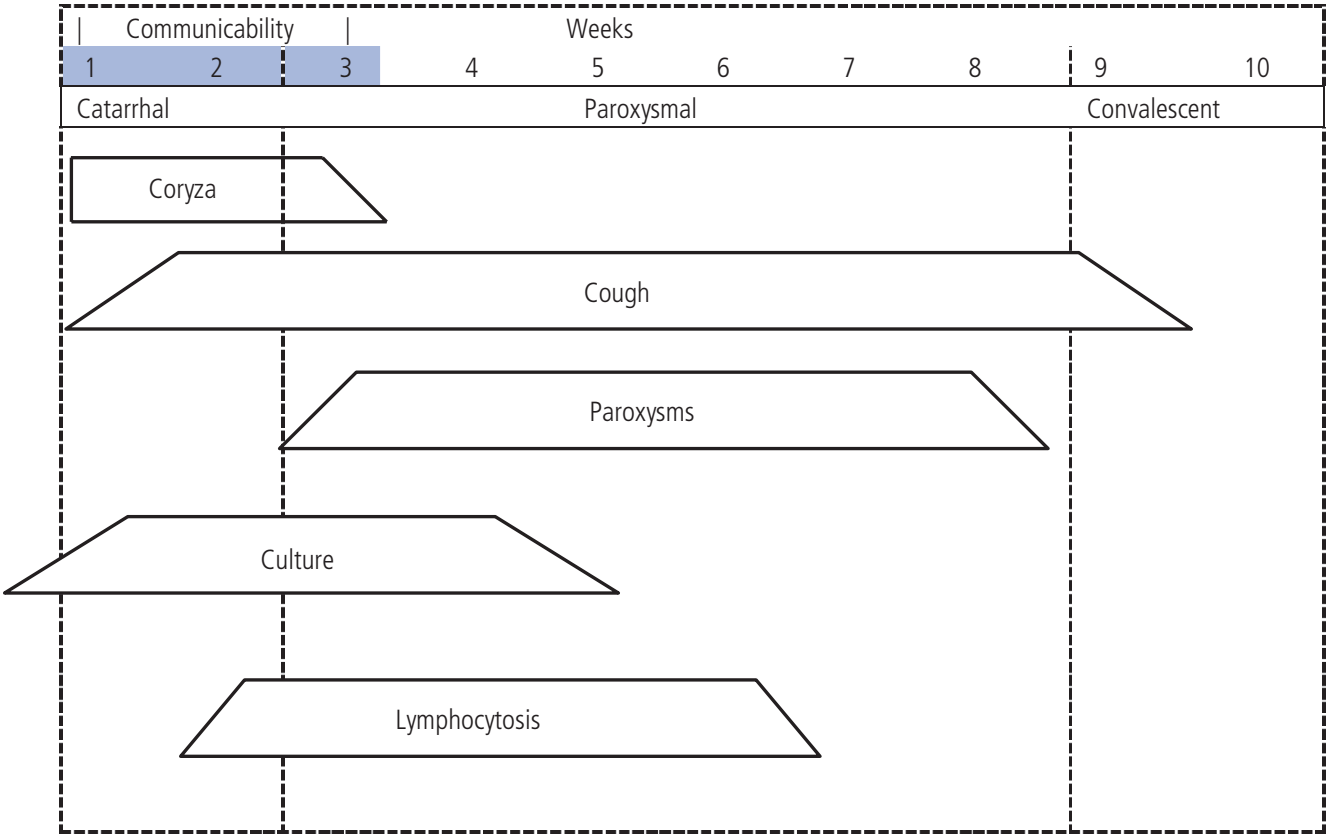
Figure 5. Infant with pertussis.

Credit: Courtesy of Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital, Hong Kong.

The clinical course of the disease can be divided into the following three stages:

- **Catarrhal stage.** The first stage of disease is insidious and mimics a minor upper respiratory tract infection. Manifestations include coryza (runny nose), sneezing, low-grade fever, and a mild, occasional cough. The cough progresses over one to two weeks and becomes paroxysmal.
- **Paroxysmal stage.** This stage is characterized by severe episodes of paroxysmal cough, apparently as a result of the difficulty in expelling thick mucus from the tracheobronchial tree. In this stage, a long inspiratory effort, usually accompanied by a high-pitched whoop and/or vomiting, follows the paroxysm and the patient can become cyanotic. Cyanosis and apnea following the paroxysm and a very ill appearance are more common in young infants during this stage (Figure 5). However, patients can appear normal between paroxysms.
- **Convalescent stage.** After reaching a peak of frequency and severity, the paroxysms of cough gradually subside, rarely lasting more than two to six weeks. However, a nonparoxysmal cough can persist for several weeks (see Figure 6).

Figure 6. Diagram of the clinical course of "classic" pertussis.



Source: Adapted from Morley D. *Pediatric priorities in the developing world*. The English Language Book Society and Butterworth. Butterworth & Co, Ltd: London, England, ©1980:237, with permission from Elsevier.

"Classic" pertussis is more common among infants 6 months of age or older and in young children. Infants aged less than 6 months have the highest case-fatality rates; cyanosis and dyspnea are more marked and, in some cases, are the main manifestations of the disease, as these infants may not present with pertussis paroxysms. Adolescents and adults may present with prolonged cough accompanied or not by paroxysms, sleep disturbance, expectoration, and vomiting. Mild and/or atypical cases occur mostly among adolescents and adults (*14*, *17*, *18*).

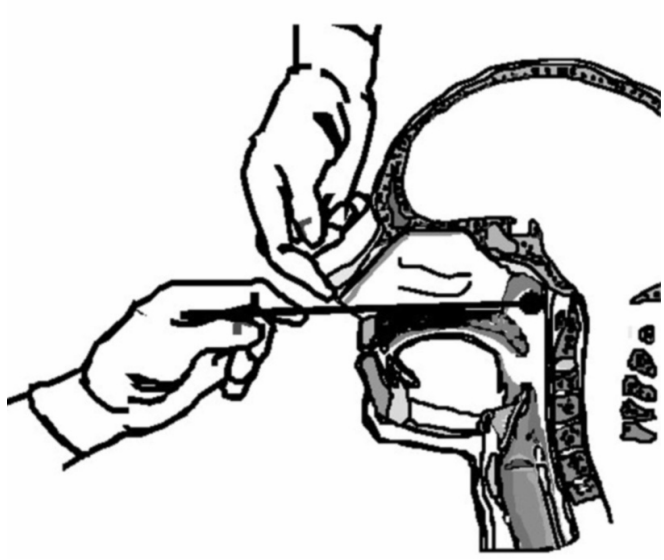
2.3.3 Laboratory Diagnosis

The laboratory confirmation of pertussis cases remains a challenge, even during pertussis outbreaks. Isolation of *B. pertussis* by culture is the standard and preferred laboratory test for the diagnosis of the disease. An elevated white blood cell count with lymphocytosis is usually present in severe cases among young infants (*18*).

Culture. *B. pertussis* is a fastidious bacterium that is usually difficult to isolate (*19*). The ability to obtain a positive culture result from a person with pertussis can be affected by several factors:

- How the specimen is handled;
- The stage of illness at the time of specimen collection;
- The use of antimicrobial therapy prior to culture;
- Immunity derived from past infection or from vaccination; and
- Age of the patient.

Figure 7. Proper technique for obtaining a nasopharyngeal specimen for isolation of *B. pertussis.*



Source: Centers for Disease Control and Prevention.

Specimen collection and handling (*17*). Specimens from the posterior nasopharynx, not the throat, should be collected using a swab or by aspiration. The Dacron or calcium alginate swab (non-cotton) should be introduced slowly through the nostril and kept for about 10 seconds in the pharynx before inoculating the media (Figure 7). Nasopharyngeal aspirates are preferred, especially if the sample also will be used for the polymerase chain reaction (PCR) test. The aspirates can be collected using a small tube (e.g., an infant feeding tube) connected to a mucous trap that is inserted into the nostril to the posterior pharynx, using a similar approach to the one shown in Figure 7. Secretions are aspirated while the tube is in that position, and while partly withdrawing it. Inoculating the secretions directly into a specialized culture medium for pertussis (Bordet-Gengou) at the bedside increases the yield of positive cultures. If that is not possible, the Regan-Lowe medium can be used for transport, though the likelihood of isolation might be compromised.

Cultures of samples collected during the catarrhal stage have a higher success rate, as do samples collected prior to the use of antibiotics against pertussis (erythromycin or trimethoprim-sulfamethoxazole). Lower rates of positive cultures have been seen from vaccinated and older persons.

Polymerase Chain Reaction (PCR) Test. PCR for pertussis can be rapid, specific, and sensitive. Although bacteria cannot be cultured after five days of antibiotic therapy, PCR can remain positive for an additional week. If available, PCR may be used in addition to culture.

Direct Fluorescent Antibody (DFA) Test. DFA testing is sometimes used as a screening test for pertussis. However, DFA tests lack sensitivity for *B. pertussis*, leading to false-negative results. They also have variable specificity, as there are some cross-reactions with normal nasopharyngeal flora. DFA testing should not be used as a criterion for pertussis diagnosis.

Serologic Tests. Several tests to measure serum antibodies to *B. pertussis*, including enzyme-linked immunosorbent assays (ELISAs), have been used in investigation, but they are not yet widely available for routine clinical use. A significant rise in antibody titers between an acute-phase specimen and a convalescent-phase specimen suggests infection. However, a significant rise in antibody titers may not be seen because the first specimen usually is taken late in the course of the infection due to the insidious onset of pertussis (*14*).

LABORATORY TESTS FOR PERTUSSIS

Bacteriological culture:
• Is the standard and preferred laboratory test for pertussis confirmation. However, isolation of *Bordetella pertussis* is difficult and is affected by several factors:
- Collection and handling of specimens;
- Stage of illness at specimen collection;
- Prior use of antibiotics;
- Age and vaccination status of the case.
Polymerase chain reaction (PCR) test:
• Is a rapid, specific, and sensitive test for detecting *B. pertussis* antigens;
• Is usually used in addition to bacteriologic culture because it is not widely available and not well standardized.
Direct fluorescent antibody (DFA) test:
• Is sometimes used as a screening test for pertussis. However, it lacks sensitivity and has variable specificity.
Serologic test:
• Is potentially useful if a significant rise in antibody titers is observed between acute and convalescent samples. However, this test is not widely available.

2.3.4 Differential Diagnosis

The differential diagnosis for pertussis includes respiratory infections of various etiologies and parapertussis, though this latter disease is usually less severe. The catarrhal stage and pertussis among adolescents and adults can be indistinguishable from other upper respiratory infections. In young infants, the differential diagnosis includes other causes of episodic cyanosis or apnea.

2.3.5 Complications

Case-fatality rates for pertussis vary in different settings but are consistently higher in infants aged less than 6 months, children with enteric and respiratory infections, and malnourished children.

Complications include (*14*, *16*):

- Pneumonia, which is the most common cause of pertussis-related deaths;
- Neurological alterations, including seizures and encephalopathy with altered consciousness;
- Nutritional problems and dehydration, mainly due to vomiting, but that can also be due to increased caloric utilization and inadequate feeding practices for sick children;
- Complications resulting from the pressure of severe paroxysms of cough, such as subconjuctival hemorrhages, epistaxis, edema of the face, pneumothorax, subdural hematomas, hernias, rectal prolapse, and, in adults, urinary incontinence and even rib fractures;
- Secondary bacterial infection which can cause pneumonia, otitis media, or sepsis.

2.3.6 Treatment

The management of pertussis cases consists of antibiotics, supportive measures, and isolation.

Antibiotics. The main value of using antibiotics is to limit the period of communicability. Additionally, the antimicrobial treatment of pertussis cases may decrease the severity of the symptoms if treatment is given in the catarrhal stage or early paroxysmal stage. Erythromycin (40–50 mg/kg/day, orally, divided in four doses; maximum 2 g/day) is the antibiotic of choice, and is given for 14 days.

Studies suggest that *B. pertussis* is susceptible to azithromycin (10–12 mg/kg/day, orally, in one dose for five days; maximum 600 mg/day) and clarithromycin (15–20 mg/kg/day, orally, divided in two doses for seven days; maximum 1 g/day). Azithromycin and clarithromycin may be as effective as erythromycin and have better compliance (*16*).

Isolation. Known pertussis cases should be placed in respiratory isolation. Suspected cases should avoid contact with young children and infants, especially unimmunized ones. Isolation can be terminated after the first five days of anti-pertussis antibiotic therapy; otherwise, patients should be isolated for three weeks.

2.3.7 Management of Contacts

The main goal of managing pertussis contacts is to prevent the disease in infants.

Management of close contacts includes antibiotics, vaccination, and quarantine.

- **Antibiotics.** A 14-day course of erythromycin or trimethoprim-sulfamethoxazole, regardless of immunization status and age (*14*). Azithromycin and clarithromycin are potential alternatives for persons who cannot tolerate erythromycin (*16*).

- **Vaccination.** Even though immunization against pertussis is not protective for contacts of pertussis cases, vaccination is recommended to limit the spread of the disease in the affected community. Children aged less than 7 years who have not received the primary series should be immunized, observing the minimum intervals between doses. Those children who have not received a dose within the previous three years should be vaccinated as soon after exposure as possible (*15*).
- **Quarantine.** Inadequately vaccinated contacts aged less than 7 years should be quarantined by excluding them from child-care centers, schools, and public gatherings for 21 days after exposure, or until cases and contacts have received five days of their 14-day antibiotic course (*16*).

2.4 VACCINATION ACTIVITIES

2.4.1 Routine Immunization

The priority goal for pertussis control for every country should be to achieve at least 95% coverage with three primary doses of pentavalent vaccine among 1 year old children in each municipality (*10*).

2.4.2 Outbreak Control

Case-fatality rates from pertussis are high in infants aged less than 1 year and highest in those aged less than 6 months. In the event of an outbreak, these children need to be, identified, monitored, and treated appropriately. Efforts should be made to confirm an outbreak by obtaining laboratory confirmation in at least some of the probable cases. To prevent the spread of the disease, antibiotic prophylaxis of all contacts is essential. Closure of schools and other settings where children congregate may be necessary. During pertussis outbreaks, the vaccination status of all children aged between 1 and 6 years should be reviewed and vaccine given, if indicated. The benefits of accelerating the schedule for infants should be considered.

As for diphtheria outbreaks, the creation of *ad hoc* committees to review pertussis case data during an outbreak could be useful to improve case management, case notification, and epidemiological investigation.

3 TETANUS

[ICD-9 037; ICD-10 A35]
[Obstetrical tetanus: ICD-10 A34]
[Neonatal tetanus: ICD-9 771.3; ICD-10 A33][a]

3.1 INTRODUCTION

Tetanus is an acute disease caused by the toxin produced by *Clostridium tetani*. It is frequently fatal and is characterized by progressive muscular rigidity and convulsive spasms of the skeletal muscles.

Control of tetanus has been a general strategy pursued within the goals of the immunization programs in the Americas. Although a goal has never been established for its eradication, its incidence has declined significantly. Several factors have contributed to this reduction: the strengthening of the health services of the Western Hemisphere; the progressive increase in DPT coverage in childhood; vaccination of children with tetanus toxoid at schools; and the effort to eliminate neonatal tetanus, which was initiated in the 1980s. The strategy of eliminating neonatal tetanus as a public health problem, in addition to promoting childbirth under hygienic conditions, gave rise to specific efforts to vaccinate all women of childbearing age who live in areas at risk for neonatal tetanus. The strategy consisted of identifying municipalities with cases of neonatal tetanus, identifying the target population (women of childbearing age, usually between 15 and 49 years of age), and vaccinating them with at least two doses of tetanus toxoid (*20*).

3.2 EPIDEMIOLOGY[b]

3.2.1 Infectious Agent

C. tetani is an anaerobic, Gram-positive bacillus that can develop a terminal spore. The organism is sensitive to heat and cannot survive in the presence of oxygen. The spores, however, are very resistant to heat and to antiseptics in daily use. They can survive in an autoclave at 121°C for 10 to 15 minutes. They are also very resistant to phenol and other chemical agents (*21*).

3.2.2 Occurrence

The spores are distributed worldwide in the soil and in the intestines of horses, cows, sheep, cats, rats, and chickens. Soil contaminated by excreta from these animals or

[a]For neonatal tetanus, please consult Pan American Health Organization, *Neonatal Tetanus Elimination Field Guide* (Scientific and Technical Publication No. 602; Washington, D.C.: PAHO, 2005).
[b]See Annex 1, "Summary of the epidemiological characteristics of diphtheria, pertussis, tetanus, *Haemophilus influenzae* type b (Hib), and hepatitis B."

treated with manure fertilizers contains large numbers of spores. In agricultural areas, adults can also harbor spores in their digestive tracts. The spores have also been found on skin and as contaminants of heroin (*21*).

3.2.3 Transmission

C. tetani usually enters the body through a wound (apparent or inapparent). However, cases have been reported after surgeries, dental extractions, burns, otitis media, animal bites, and abortions (*20, 21*).

3.2.4 Reservoir

The principal reservoirs of *C. tetani* are the intestinal tracts of humans and animals and soil used for agriculture or livestock or products obtained from excreta of horses, cows, sheep, cats, rats, and chickens (*21*).

3.2.5 Incubation

The incubation period ranges from 3 to 21 days, and is usually around 8 days. In general, the farther the introduction site of the spores from the central nervous system, the longer the incubation period. Mortality is directly proportional to the length of the incubation period, with shorter periods associated with higher mortality. In neonatal tetanus, symptoms usually appear between 4 and 14 days after birth, with an average of 7 days.

3.2.6 Communicability

Tetanus cannot be transmitted from one person to another. It is one of the few vaccine-preventable diseases that is infectious but not contagious (*21*).

3.2.7 Immunity

The disease does not confer immunity. Immunity is acquired passively through maternal antibodies or actively through injection of tetanus toxoid.

3.2.8 Changing Epidemiology

There have not been significant changes in the general epidemiology of tetanus in adults. The disease continuously occurs in unvaccinated populations at risk of wounds and in places where there are *C. tetani* spores, that is, in rural, poor, livestock-raising areas with populations that do not have adequate health services.

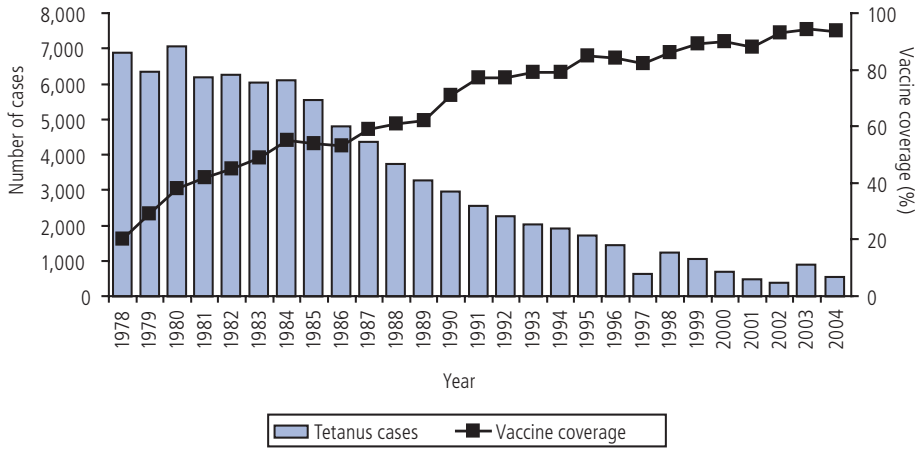
As mentioned earlier, the strategy employed to eliminate neonatal tetanus has contributed to tetanus prevention in general. The reduction in incidence has been dramatic in the Americas. More than 7,000 cases of tetanus were reported in 1980, but only 598 cases were reported in 2004 (see Figure 8). Neonatal tetanus has been eliminated as a public health problem in most of the Region, with most of these cases now occurring in Haiti.

3.3 CLINICAL ASPECTS

3.3.1 Pathogenesis

C. tetani usually enters the body through a wound. Under anaerobic conditions (very low levels of oxygen), the spores germinate, producing toxins, including tetanospasmin, that are disseminated throughout the organism by blood and lymph. The toxins act on different levels in the central nervous system, including the peripheral motor nerves, spinal cord, brain, and sympathetic nervous system. The typical clinical manifestations of the disease begin when the toxin interferes with the release of neurotransmitters, blocking those responsible for inhibiting nerve impulses. This leads to muscle contractions and spasms. Convulsions can also occur and the autonomic nervous system can be affected (*21*).

Figure 8. Annual incidence of tetanus and DPT3 vaccine coverage among children aged less than 1 year, Region of the Americas, 1978–2004.



Source: Pan American Health Organization, Family and Community Health Area, Immunization Unit.

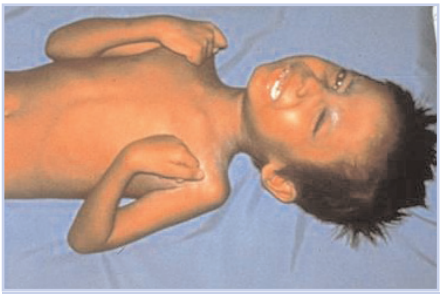
3.3.2 Clinical Features

Three different forms of tetanus can be characterized: local, cephalic, and generalized (*21*).

- **Local tetanus** is a very rare form of the disease in which the patients have persistent muscle contractions in the same anatomical area as the wound or injury. The contractions can persist for many weeks before disappearing. Local tetanus can precede generalized tetanus. Approximately 1% of these cases are fatal.
- **Cephalic tetanus** is also a rare form of the disease, occurring occasionally in association with otitis media or following a head wound. The cranial nerves, especially facial ones, can be compromised.
- **Generalized tetanus** is the most common form of the disease, accounting for approximately 80% of cases. The disease usually occurs with a descending pattern. The initial sign is trismus ("lockjaw," or spasm of the jaw muscles), followed by rigidity of the neck, difficulty swallowing, and rigidity of the abdominal muscles. Other symptoms include an increase in temperature, perspiration, an increase in blood pressure, and episodes of tachycardia. Spasms can last several minutes and may persist for three or four weeks. Total recovery can take months.

In neonatal tetanus, which is a generalized form of tetanus, the clinical manifestations are seen within 3 to 28 days of birth and consist of (*22*):

- Cessation of breast-feeding (the first sign in a newborn) because of difficulty in grasping and sucking the nipple, usually beginning on at age 3 days;
- A characteristic position in which the legs are extended and the arms folded toward the chest, with the hands kept closed due to difficulty in opening them;
- Generalized contractual crises leading to opisthotonus, which last a few minutes. Between these spasms, the child appears normal (see Figure 9).



Credit: Centers for Disease Control and Prevention

Figure 9. Child with opisthotonus.

3.3.3 Laboratory Diagnosis

Laboratory confirmation of tetanus is generally difficult. The organism is rarely recovered from the site of infection and usually there is no detectable antibody response.

3.3.4 Differential Diagnosis

The most common differential diagnoses are sepsis, meningoencephalitis, tetany with other causes, peritonitis, and inflammatory processes of the external ear or of the oral region, accompanied by trismus.

3.3.5 Complications

Complications of tetanus include (*21, 23*):

- Laryngospasms (spasms of the vocal cords and/or the respiratory muscles);
- Fractures of the spinal column or of the tubular bones as a consequence of prolonged contractions and convulsions;
- Hyperactivity of the autonomic nervous system, which can lead to hypertension and tachycardia;
- Nosocomial infections, which are frequent due to prolonged hospitalization;
- Secondary infections, which can include sepsis, pneumonia, and decubitus ulcers;
- Pulmonary embolisms, especially in the elderly;
- Pneumonias, including aspiration pneumonia; and
- Death, which in neonatal tetanus can occur in 10%–90% of cases that receive treatment, and nearly 95% of untreated cases.

3.3.6 Treatment

Treatment includes wound management, antibiotics, treatment with tetanus antitoxin, keeping the respiratory passages clear, and supportive measures to control spasms.

Wound Management (*24*) Wounds should be properly cleaned and debrided if dirt or necrotic tissue is present. Additionally, active immunization with tetanus toxoid and tetanus immune globulin should be considered (see Table 3).

Antibiotics (*24*) A 10 to 14 day-course of oral (or IV) metronidazole (3 mg/kg per day, given at six hour intervals; maximum 4 g per day) is recommended because it decreases the number of vegetative forms of *C. tetani*. Penicillin G may be used as an alternative.

Tetanus Immune Globulin (TIG) It is recommended that human tetanus immune globulin (TIG) be administered to individuals with tetanus. TIG removes the tetanus toxin that is still not bound to the tissues; it does not affect the toxin that is already bound to the nerve endings. Children and adults should receive a single IM dose of 3,000–5,000 units, with part of the dose infiltrated around the wound (*21*).

If human tetanus immune globulin is not available, tetanus antitoxin of equine origin can be used.

Table 3. Summary guide to tetanus prophylaxis in routine wound management

History of vaccination with absorbed tetanus toxoid (doses)	Clean, minor wounds		All other wounds[a]	
	Td[b]	TIG[c]	Td[b]	TIG
Unknown or < 3	Yes	No	Yes	Yes
≥ 3[d]	No[e]	No	No[f]	No

[a] Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from crushing, burns, and frostbite.
[b] Td = adult-type toxoid and tetanus diptheria vaccine. For children < 7 years old, DPT (DT, if pertussis vaccine is contraindicated) is preferred to tetanus toxoid alone. For persons ≥ 7 years of age, Td is preferred to tetanus toxoid alone.
[c] TIG = human tetanus immune globulin.
[d] If only three doses of fluid toxoid have been received, then a fourth dose of toxoid, preferably an adsorbed toxoid, should be given.
[e] Yes, if > 10 years since last dose.
[f] Yes, if > 5 years since last dose. More frequent boosters are not needed and can accentuate adverse events.

Source: Adapted from American Academy of Pediatrics. Tetanus (Lockjaw). *In*: Pickering LK, ed. *Red book: 2003 report of the Committee on Infectious Diseases*, 26th ed. Elk Grove Village, IL: American Academy of Pediatrics; ©2003:614, with permission.

3.4 VACCINATION ACTIVITIES

3.4.1 Routine Immunization

As with diphtheria and pertussis, it is the task of the health facilities to vaccinate the cohorts of newborns in their area of responsibility, administering the primary series according to the immunization schedule to achieve at least 95% coverage in all municipalities (*10*). In order to prevent neonatal tetanus, all women of childbearing age should be immunized, and adequate vaccination of pregnant women should be confirmed.

3.4.2 Other Vaccination Activities

Tetanus disease does not confer immunity, and, for this reason, recovering patients should be vaccinated following the regular schedule (*20, 21*).

All groups who for occupational reasons are exposed to *C. tetani* are considered at risk. All newborns also are considered at risk, since they can contract tetanus during delivery or during the first days of life if the mother is not adequately protected. It is recommended that all women of childbearing age be vaccinated, as newborns cannot be vaccinated with tetanus toxoid and it is generally impossible to predict the circumstances of delivery and postnatal care (*22*).

3.4.3 Outbreak Response

Outbreak response is not applicable to tetanus. However, if a cluster of cases of neonatal tetanus is reported, active case search and investigation is indicated. Poor birth attendant practices may increase the likelihood of additional cases in the community where that birth attendant works.

4 *HAEMOPHILUS INFLUENZAE* TYPE B

[*Haemophilus* meningitis ICD-9 320.0; ICD-10 G00.0]

4.1 INTRODUCTION

Invasive infections by *Haemophilus influenzae* type b (Hib) are a major cause of bacterial meningitis and of lower respiratory infections in children, and a significant contributor to mortality in children aged less than 5 years. Worldwide, it is estimated that Hib infections cause at least three million cases of severe disease per year and between 400,000 and 700,000 children die annually due to Hib disease (*25*).

4.2 EPIDEMIOLOGY[a]

4.2.1 Infectious Agent

Haemophilus influenzae type b (Hib) is a Gram-negative coccobacillus, usually aerobic, which requires chocolate agar as its culture medium for growth in the laboratory.

There are two varieties of *Haemophilus*: the encapsulated strains, among which Hib is the most pathogenic, and the acapsular strains, which are usually non-invasive and less pathogenic but responsible for frequent otorhinolaryngeal infections (e.g., otitis, epiglottitis, bronchitis, superinfections of the respiratory tract).

Haemophilus influenzae has six polysaccharide capsular serotypes but serotype b is responsible for more than 95% of the invasive processes and the only one prevented by vaccination. Its external capsule consists of a polysaccharide—polyribosylribitol phosphate (PRP)—which is responsible for the organism's virulence and for immunity (*26*).

4.2.2 Occurrence

Haemophilus influenzae type b is distributed worldwide and primarily affects children aged 2 months to 3 years. The disease is uncommon in children aged over 5 years. Secondary cases are sometimes observed in families and in child-care centers.

4.2.3 Transmission

Hib is transmitted from one person to another through the respiratory tract by means of aerosolized droplets.

4.2.4 Reservoir

Humans are the only reservoir of the bacteria.

4.2.5 Incubation

The exact incubation period is unknown but probably lasts from two to four days.

[a]See Annex 1, "Summary of the epidemiological characteristics of diphtheria, pertussis, tetanus, *Haemophilus influenzae* type b (Hib), and hepatitis B."

4.2.6 Communicability

Hib is communicable while the microorganisms are present, even if there are no nasal secretions. The disease ceases to be communicable 24–48 hours after beginning treatment with antibiotics (*27*).

4.2.7 Immunity

Infection by Hib is age dependent. The maternal immunoglobulin G (IgG) antibodies transferred via the placenta and breast-feeding confer a certain degree of protection during the first 2 to 6 months of life. At this age, an infant's immune system is too immature to generate an adequate response to the polysaccharide antigens of the external capsule of Hib, which explains the increase in the number of cases once passive natural protection declines. Starting at 2 years of age, the immune system matures and can generate protective responses.

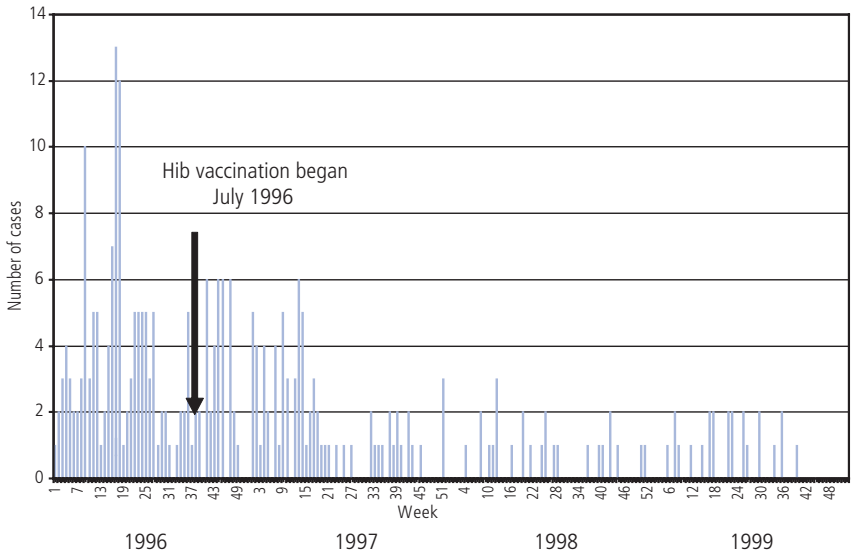
During the pre-vaccine era, most children acquired natural immunity by 5 to 6 years of age through inapparent infection by Hib. In view of the fact that only a relatively small proportion of children of any age are carriers of Hib, it has been postulated that exposure to organisms that have the same antigenic structure as the Hib capsule (i.e., organisms that cross-react) promotes development of antibodies against that capsule. Natural exposure to Hib also induces formation of antibodies against the external protein membrane, lipopolysaccharides, and other antigens on the surface of the bacterium.

4.2.8 Changing Epidemiology

Before the introduction of effective vaccines against Hib, this organism was the leading cause of bacterial meningitis and other invasive diseases, such as sepsis, pneumonias, arthritis, and osteomyelitis in children aged less than 5 years. Estimations of the Hib incidence rate during the pre-vaccine era ranged from 50 to 150 cases per 100,000 children in this age group. When vaccination against Hib is introduced, most cases occur in infants and children who are not vaccinated or are incompletely vaccinated. The highest rate of invasive disease caused by Hib tends to occur among infants who have still not reached vaccination age (6 months). The incidence among children aged 1 to 4 years is much lower than among infants aged less than 1 year. Case-fatality currently ranges from 2% to 5%, depending on the country, with 15%–30% of survivors presenting with sequelae (*28*).

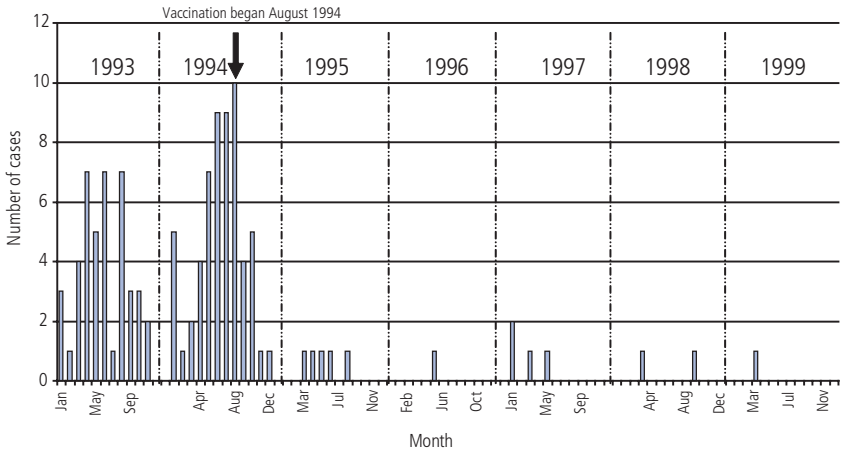
In countries of the Americas that introduced the vaccine in the mid-1990s, such as Uruguay and Chile, a significant reduction of cases of invasive disease by *H. influenzae* type b has been observed (Figures 10 and 11). Chile uses a three-dose schedule and Uruguay a four-dose series, which, considering the effectiveness of the vaccine in relation to the number of doses administered, could explain some differences in the degree of impact for each country (*25*, *29*). Whether a three or four dose schedule is used, the impact has been extraordinary.

Figure 10. Cases of invasive disease by *Haemophilus influenzae* type b, Chile, 1996–1999.



Source: Pan American Health Organization, Family and Community Health Area, Immunization Unit.

Figure 11. Cases of meningitis by *Haemophilus influenzae* type b, Uruguay, 1993–1999.



Source: Pan American Health Organization, Family and Community Health Area, Immunization Unit.

4.3 CLINICAL ASPECTS

4.3.1 Pathogenesis

The organism enters the human body through the nasopharynx, colonizes the nasopharynx, and can remain up to a few months without causing disease (asymptomatic carriage). In general, 1% to 5% of healthy children carry Hib without suffering from the disease (*28*, *30*).

In the invasive processes, Hib passes from the nasopharynx to the blood, causing infection at distant sites, especially the meninges. Viral infections are thought to facilitate the invasion. Overcrowding, large households, attendance at child-care centers, low socioeconomic level, low educational status, and school-age siblings increase a child's risk of contracting Hib. Patients with chronic diseases and certain ethnic groups (e.g., Eskimos and blacks) also are more susceptible to infection (*26*, *28*, *30*).

4.3.2 Clinical Features

The invasive disease caused by Hib occurs in several clinical forms. Meningitis is the infection of the membranes that cover the brain and is the most common clinical manifestation of invasive infections by Hib, accounting for approximately 50% to 65% of cases of meningitis during the pre-vaccine era (*25*).

Other frequently occurring forms of invasive Hib are epiglottitis, septic arthritis, cellulitis (infection of the skin and soft tissues), and unifocal or multifocal pneumonia, with or without effusion. Osteomyelitis and pericarditis are less frequent.

Otitis media is usually caused by non-b strains of *Haemophilus influenzae* and cannot be prevented with the vaccine.

4.3.3 Laboratory Diagnosis

Laboratory diagnosis is made through isolation of Hib from normally sterile fluids, such as cerebrospinal fluid (CSF), pleural fluid, blood, and joint fluid, and aspirate from the middle ear. Positive culture of such samples in chocolate agar and the presence of the Gram-negative coccobacillus confirm the diagnosis of disease caused by Hib. Serotyping can be done in isolates of *Haemophilus influenzae* to determine if it is type b, the only serotype that is potentially vaccine-preventable.

Antigen detection in the aforementioned body fluids can help facilitate the diagnosis in patients partially treated with antibiotics. Latex particle agglutination and countercurrent immunoelectrophoresis are two useful serological methods for antigen detection; the former is more rapid, sensitive, and specific (*31*).

4.3.4 Differential Diagnosis

Because the incidence of bacterial meningitides is high, differential diagnosis of meningitis and *Haemophilus influenzae* type b should be conducted for every child with fever who presents altered mental state, irritability, or evidence of other neurological dysfunction. The most frequent differential diagnoses involve meningitides caused by *Neisseria meningitidis* (meningococcus) and *Streptococcus pneumoniae* (pneumococcus), although several infectious agents can cause widespread infection of the central nervous system with clinical manifestations similar to those of Hib (*27*).

In any case of pneumonia with consolidation on the X-ray image, *Haemophilus influenzae* type b should be included in the differential diagnosis.

Clinically, no difference can be established among meningitides or bacterial pneumonias caused by different bacteria.

4.3.5 Complications

The most frequent complications of meningitis are convulsions, increase in intracranial pressure, paralysis of the facial nerves, cerebrovascular accidents, cerebral herniation, transverse myelitis, ataxia, thrombosis in the venous sinuses, and subdural abscesses.

Epiglottitis caused by Hib can cause death due to obstruction of the respiratory tract.

Mortality in industrialized countries ranges from 2% to 5%, regardless of the antimicrobial treatment. Severe neurological sequelae (hearing disorders, delay in language acquisition, developmental delay, motor abnormalities, visual impairment, and behavior abnormalities) occur in 15% to 30% of those who survive (*28*, *30*).

4.3.6 Treatment (27, 32)

Specific treatment with antibiotics is necessary for invasive disease caused by Hib. Ceftriaxone, cefotaxime, or ampicillin combined with chloramphenicol should be administered until the sensitivity of the organism is determined. Intravenous antibiotics are usually given for 10 days, but longer therapy may be indicated for complicated cases. The drug of choice used to be ampicillin; however, considering that up to 30% of Hib strains are resistant through production of β-lactamase, ampicillin alone is no longer the first option. To ensure the elimination of the organism, rifampicin should be administered before the patient leaves the hospital.

Concurrent quarantine is not needed.

4.3.7 Management of Contacts (27, 32)

In investigating the contacts and the source of infection, all children less than 6 years of age should be observed carefully, especially infants. Observation should be attentive to the signs of the disease, especially fever.

Contacts should receive chemoprophylaxis, since it is effective in preventing secondary transmission of Hib. In homes where, in addition to the index case, there are infants aged less than 12 months, immunodeficient children, or inadequately immunized 1 to 3 year old children, treatment with oral rifampicin is recommended for all contacts in the family unit (once a day for four days at a dosage of 20 mg/kg; a maximum dose of 600 mg/day).

Employees and other children in the rooms or classes in child-care centers or kindergartens where a case occurs also should be treated as above. The protective levels of antibodies after vaccination are not reached until the end of the first week; therefore, a vaccinated child exposed to the disease during that time still runs the risk of acquiring the disease while he or she develops antibodies.

4.4 VACCINATION ACTIVITIES

The principal objective of vaccination against Hib is to prevent the serious diseases caused by the bacterium in infants and young children.

4.4.1 Routine Immunization

Universal vaccination of infants with the primary series of vaccine against Hib[b] has proven to be effective and should be a priority in the routine activities of the EPI (*25*). The objective is to achieve at least 95% coverage in children aged less than 1 year in all municipalities with Hib or pentavalent (*10*). Routine vaccination against Hib is generally given at the same age as DPT, either in combination or in separate injections. Some countries give a booster following the primary three-dose series.

4.4.2 Other Vaccination Activities

Those at risk for Hib infection generally include people with underlying cardiopulmonary conditions; persons with chronic diseases, such as asthma, cystic fibrosis, cardiopulmonary malformations, immune deficiencies, renal insufficiency, and sickle cell anemia; patients undergoing treatment for cancer; asplenics; and patients infected with the human immunodeficiency virus (HIV), although in these patients immunogenicity varies according to the degree of infection. Some patients with special conditions, such as malnutrition, tuberculosis, or debilitating diseases, could also be considered at risk for Hib infection and should benefit from timely, systematic administration of the vaccine.

[b]For more details on the Hib immunization schedule see Section 7.2 on Hib in Chapter 7 of this guide.

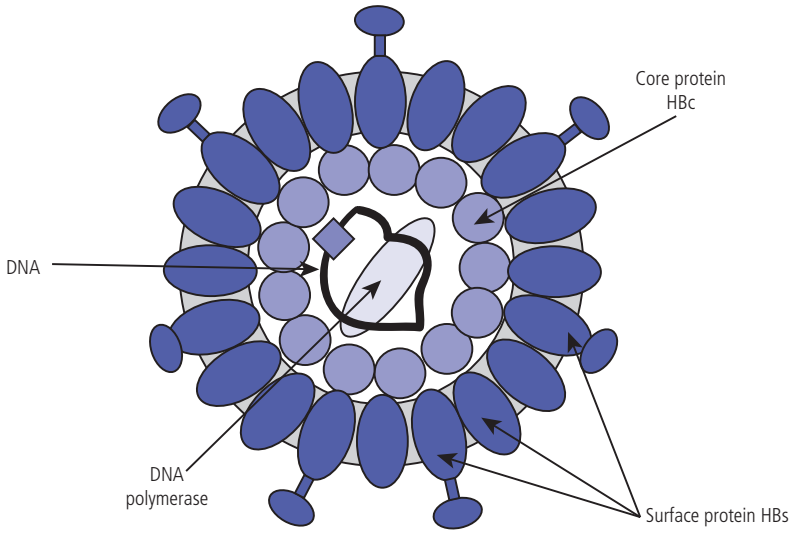
5 HEPATITIS B

[ICD-9 070.3; ICD-10 B16]

5.1 INTRODUCTION

Infection with the hepatitis B virus (HBV) is estimated to affect some two billion people worldwide, of whom some 360 million have a chronic infection with a high risk of sequelae, such as liver failure, cirrhosis, or liver cancer (*33*). HBV may be the cause of up to 80% of the cases of liver cancer throughout the world, and is second to tobacco among known carcinogens (*34*, *35*).

Figure 12. Hepatitis B virus.



Source: Millinship S. Hepatitis B virology and immunology [Internet site]. Available at: http://www.hon.ch/Library/Theme/HepB/virology.html. Accessed on 24 December 2004.

5.2 EPIDEMIOLOGY[a]

5.2.1 Infectious Agent

Hepatitis B virus is a DNA virus belonging to the family Hepadnaviridae. Its principal components are the surface antigen (HBsAg), previously called Australia antigen; the core antigen (HBcAg); and the e antigen (HBeAg). Figure 12 shows a diagram of HBV.

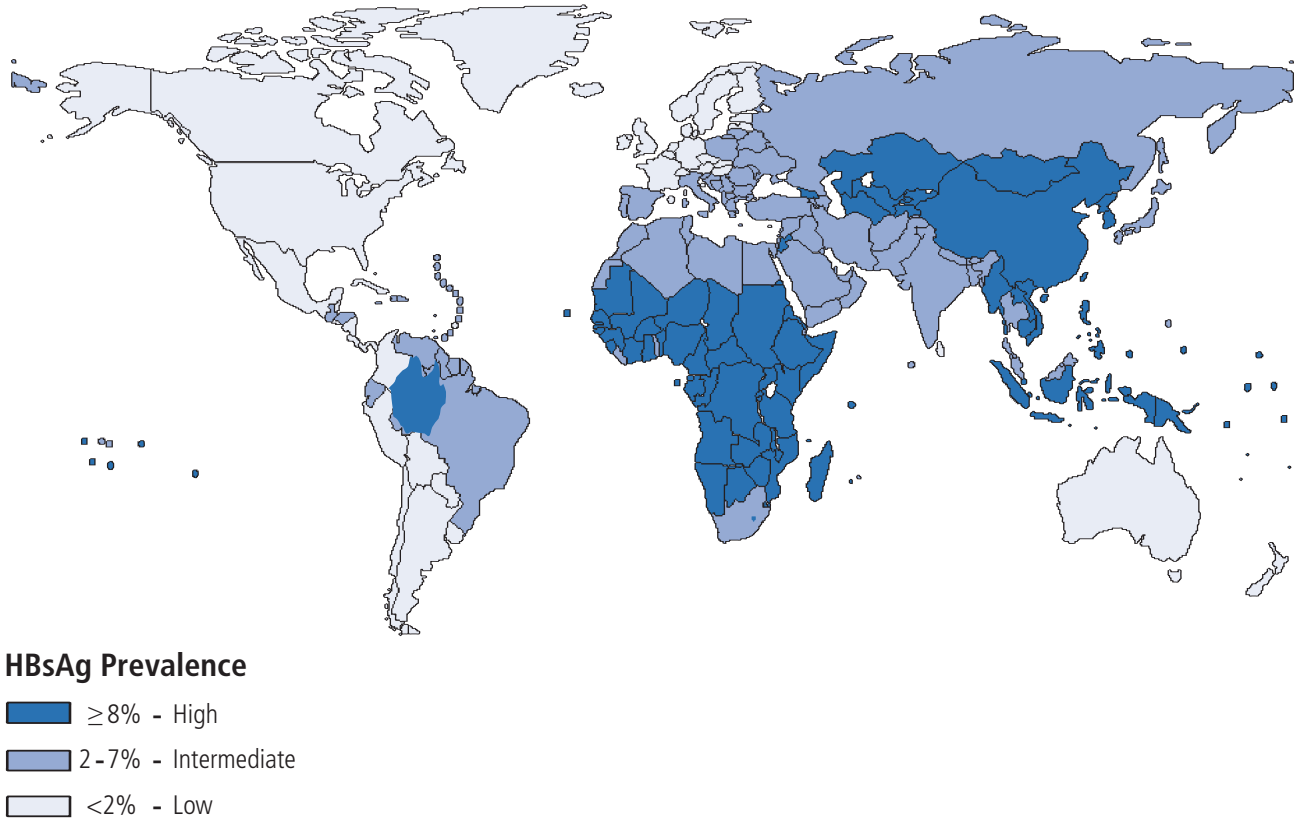
5.2.2 Occurrence

Hepatitis B is endemic throughout the world, with few seasonal variations. According to the World Health Organization (*36*), approximately 45% of the world population lives in areas where the prevalence of HBV is high (8% or more of the population is HBsAg-positive), 43% live in areas of intermediate endemicity (2%–7% are HBsAg-positive), and 12% live in areas of low endemicity (under 2% are HBsAg-positive) (see Figure 13).

The endemicity of HBV infection in the Americas varies from low to intermediate (*37*). In Latin America and the Caribbean, the highest prevalence rates are in the Amazon Basin (8%) and the lowest are in South America's southern cone. Great heterogeneity is observed in the proportion of carriers, which varies in relation to geographic area and ethnic distribution.

[a]See Annex 1, "Summary of the epidemiological characteristics of diphtheria, pertussis, tetanus, *Haemophilus influenzae* type b (Hib), and hepatitis B."

Figure 13. World prevalence of hepatitis B, prior to mass vaccine introduction in Latin America and the Caribbean, 1997.



Source: World Health Organization, Hepatitis B vaccine [Internet site]. Available at: www.who.int/vaccines/en/hepatitisb.shtml, data for the Western Hemisphere gathered from PAHO member countries.

5.2.3 Transmission

Transmission of HBV occurs through infected blood or other body fluids, including serous fluids; saliva; cerebrospinal fluid; peritoneal, pleural, pericardial, synovial, and amniotic fluids; and semen and vaginal secretions. The virus can survive one week or more at room temperature, so contact with contaminated objects and by percutaneous exposure, such as injection with unclean needles, are also transmission routes.

The principal modes of transmission are:

- Sexual contact;
- Household contact;
- Vertical transmission (e.g., from an infected mother to her infant);
- Use of injectable drugs; and
- Nosocomial exposure (exposure in health care settings).

Hepatitis B is considered a sexually transmitted disease. There is no fecal-oral transmission of HBV, nor is it transmitted by tears, sweat, or urine.

The likelihood of perinatal transmission of HBV to an infant is 10% in mothers who are HBsAg positive but HBeAg negative; it is 70% to 90% when the mother is both HBsAg positive and HBeAg positive (*35*). Several studies indicate that transmission in early infancy is more likely to result in chronic infections. In the Americas, the low prevalence of HBsAg in children during the first year of life and the increase in the prevalence of HBsAg and anti-HBc after the first year indicate that transmission in early infancy is more important than in the perinatal period.

5.2.4 Reservoir

Human beings are the reservoir for HBV.

5.2.5 Incubation

The incubation period usually is from six weeks to six months, with the average being 60–90 days (*34*, *38*).

5.2.6 Communicability

All HBsAg-positive individuals are infective. Infected individuals can transmit the infection from one to two months before the first symptoms appear and are infective throughout the acute course of the disease and in the chronic carrier phase, which can persist for years.

5.2.7 Immunity

Everyone is susceptible to hepatitis B. Immunity is lasting, whether obtained through the disease or through vaccine.

5.3 CLINICAL ASPECTS

5.3.1 Pathogenesis

The cellular and humoral immune responses to HBV infection are complex. Most studies suggest that HBV is not directly cytopathic to infected hepatocytes and that the cellular response to several viral proteins is correlated to the severity of the clinical disease and to virus elimination (*35*).

The chronic infection is believed to be related to a weak T-cell response against the viral antigens. Although neonatal immune tolerance to the viral antigens seems to play an important role in the persistence of the infection in newborns, the mechanism of the poor T-cell response in adults is not well understood (*35*).

5.3.2 Clinical Features

Hepatitis B is a viral disease that affects the liver. The virus produces an infection that can occur in various forms (Figure 14):

- Inapparent infection (most frequent in young children);
- Subacute disease with nonspecific (anorexia, nausea, or general discomfort) or extrahepatic symptoms;
- Clinical symptoms with the presence of jaundice; and
- Fulminant hepatitis.

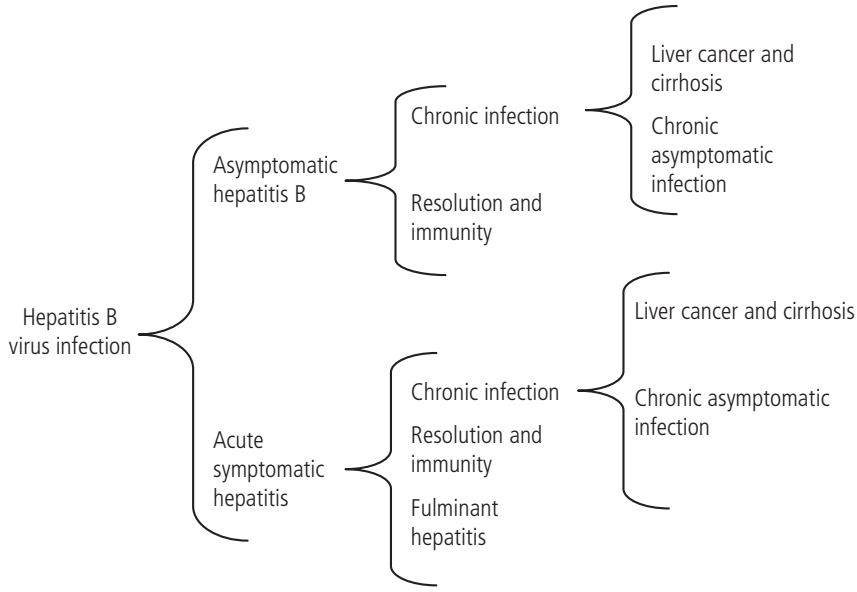
According to the signs and symptoms present, three different phases in the clinical symptoms can be identified:

- A **prodromal** or **preicteric phase**, characterized by an insidious beginning, with general discomfort, anorexia, nausea, vomiting, abdominal pains, fever, headache, myalgia, skin rash, arthralgia, and dark urine, which appear one to two days before the jaundice. This phase lasts 3 to 10 days.
- An **icteric (jaundiced) phase** of variable duration, but usually lasting from one to three weeks, with jaundice, clay-colored stools, hepatomegaly, and hepatic tenderness.
- A **convalescent phase** that lasts up to several months, with malaise and fatigue, during which the jaundice and other symptoms disappear.

Extrahepatic manifestations such as arthralgias, arthritis, maculopapular rashes, and thrombocytopenia can occur and may precede the jaundice.

It should be noted, however, that only a small proportion of acute HBV infections can be recognized clinically, because fewer than 10% of children and between 30% and 50% of adults present with jaundice. Infections in newborns are not associated with symptoms.

Figure 14. Hepatitis B virus—progression of infection.



5.3.3 Laboratory Diagnosis

Diagnosis is based on clinical, epidemiologicalal, and laboratory findings. The infection cannot be differentiated solely by clinical symptoms; definitive diagnosis depends on the results of serologic tests (see Table 4) (*34*).

Detection of Hepatitis B Surface Antigen (HBsAg). Detection of HBsAg is the most common approach to diagnosing acute hepatitis B infection or detecting carriers. HBsAg in itself is not infectious, but its presence implies that the virus is present. This antigen can be detected from as early as one or two weeks to 12 weeks after exposure. Persistence of HBsAg for six or more months defines a chronic infection (chronic carrier). The presence of antibodies to HBsAg (anti-HBs) indicates immunity.

Detection of Hepatitis B Core Antigen (HBcAg) and Antibodies to HBcAg. HBcAg is detected only in liver tissue of infected individuals and not in serum. Anti-HBc (the core antibody) indicates past infection. This antibody is not present in individuals who developed immunity through vaccination. The presence of IgM antibody to HBcAg (anti-HBc) indicates recent infection (four to six months). A negative test for

Table 4. Markers for the detection of hepatitis B infection and risk of transmission

Marker	Antigen or antibody	Interpretation	Usage
HBsAg*	Hepatitis B surface antigen	Virus present	Detection of carriers or indication of acute infection
Anti-HBs	Antibodies against the surface antigen (HBsAg)	Immunity	Identification of people who have acquired immunity through illness or vaccine
IgM anti-HBc	IgM antibodies against the virus core protein	Recent infection	Detection of acute or recent hepatitis B infection, including in persons who are HBsAg-negative. Negative results for IgM anti-HBc and positive results for HBsAg indicate chronic infection.
HBeAg	Antigen E	Active viral replication	Identification of carriers with high risk of transmitting HBsAg

*The persistence of this marker for more than six months indicates chronicity.

Source: Adapted from Centers for Disease Control and Prevention. *Epidemiology and prevention of vaccine-preventable diseases*, Atkinson W, Hamborsky J, McIntyre L, Wolfe S, eds., 8th ed. Washington, D.C.: Public Health Foundation, 2005:191–199 and American Academy of Pediatrics. Hepatitis B. In: Pickering LK, ed. *Red book: 2003 report of the Committee on Infectious Diseases*, 26th ed. Elk Grove Village, IL: American Academy of Pediatrics; ©2003:322, with permission.

Table 5. Interpretation of serologic tests for hepatitis B

Test	Result	Interpretation
HBsAg	Negative	Susceptible
anti-HBc	Negative	
anti-HBs	Negative	
HBsAg	Negative	Immunity through vaccination
anti-HBc	Negative	
anti-HBs	Positive (≥ 10 mIU/mL*)	
HBsAg	Negative	Immunity through natural infection
anti-HBc	Positive	
anti-HBs	Positive	
HBsAg	Positive	Acute infection
anti-HBc	Positive	
IgM anti-HBc	Positive	
anti-HBs	Negative	
HBsAg	Positive	Chronic infection
anti-HBc	Positive	
IgM anti-HBc	Negative	
anti-HBs	Negative	
HbsAg	Negative	May be recovering from acute HBV infection. May be distantly immune and the test is not sensitive enough to detect a very low level of anti-HBs in serum. May be susceptible with a false positive anti-HBc. May be chronically infected and have an undetectable level of HBsAg present in the serum.
anti-HBc	Positive	
anti-HBs	Negative	

*Postvaccination testing, when it is recommended, should be performed 1–2 months following dose #3.

Source: Adapted from Centers for Disease Control and Prevention, *Epidemiology and prevention of vaccine-preventable diseases*, Atkinson W, Hamborsky J, McIntyre L, Wolfe S, eds., 8th ed. Washington, D.C.: Public Health Foundation, 2005:194

IgM anti-HBc with a positive test for HBsAg indicates chronic infection.

Detection of Hepatitis B e Antigen (HBeAg) and Antibodies to HBeAg. HBeAg is detected when there are high titers of virus circulating, indicating a state of high infectivity. Antibody to HBeAg (anti-HBe) indicates low infectivity.

When interpreting serologic tests, it is important to take into account the different results at the same time. Table 5 includes the most common combinations of serological results and their interpretation.

5.3.4 Differential Diagnosis

Hepatitis is an inflammation of the liver which can be either infectious or non-infectious. Non-infectious causes of hepatitis include autoimmune, genetic, metabolic, and drug-related chemical reactions. Infectious hepatitis can be the only, or main, manifestation resulting from an infection with hepatotropic hepatitis A, B, C, D, E, or G viruses. However, it can be also one of the manifestations of a systemic or communicable illness due to agents such as cytomegalovirus, Epstein-Barr virus, adenovirus, and hemorrhagic fever viruses. In the Americas, many infectious diseases can result in jaundice, such as leptospirosis and yellow fever, to name some. The various types of hepatitis usually cannot be distinguished clinically, making laboratory detection of the serologic markers crucial.

5.3.5 Complications

Chronic Infection. Chronic infection is defined as the presence of HBsAg in serum for at least six months. It is estimated that 10% of all HBV infections progress to chronic infection. However, the risk of developing chronic HBV infection is inversely proportional to age (*34*), as follows:

- 90% for infants infected at birth;
- 30% to 50% for children infected between 1 and 5 years old; and
- 6% to 10% for adults.

Individuals with Down syndrome or with a compromised immune system, such as those with lymphoproliferative diseases, infected by HIV, or undergoing hemodialysis, apparently have a greater propensity for presenting chronic infection.

Cirrhosis and Hepatocellular Carcinoma. Cirrhosis of the liver and hepatocellular carcinomas are long-term complications of hepatitis B. It is estimated that between 15% and 25% of those with chronic HBV infection die of hepatocellular carcinoma or cirrhosis (*39*).

Fulminant Hepatitis. Fulminant hepatitis is defined as severe acute hepatitis that progresses to liver necrosis, which can be fatal. The fulminant course is also seen in pregnant women and newborns of infected mothers. Some 1%–2% of patients with acute infection present fulminant hepatitis, with mortality ranging from 63% to 93% (*34*).

5.3.6 Treatment

There is no specific treatment for acute HBV infection. Symptomatic supportive therapy is recommended. Numerous antiviral agents to prevent chronic infection have been investigated, including interferon alpha-2b, which is successful in interrupting viral replication in 25%–40% of cases (*39*).

There is no need for quarantine, although concurrent disinfection of equipment potentially contaminated with blood or other body fluids is necessary.

5.4 VACCINATION ACTIVITIES AND PASSIVE IMMUNIZATION WITH HEPATITIS B IMMUNE GLOBULIN

The main objective of the strategies to combat hepatitis B is to prevent chronic HBV infection and its serious consequences, including liver cirrhosis and hepatocellular cancer.

PAHO's Technical Advisory Group on Vaccine-preventable Diseases recommends the following for the prevention and control of hepatitis B infection (*40*):

- Routine universal infant immunization should be the primary strategy to prevent HBV transmission.
- Countries that have introduced hepatitis B (HepB) vaccine should consider using combined vaccines, either DPT+HepB or, preferably, DPT+HepB+*Haemophilus influenzae* type b (Hib) (pentavalent vaccine).
- Health care workers who are at risk of being exposed to blood or other body fluids should be routinely vaccinated.
- Vaccination coverage should be monitored on a regular basis and the impact of hepatitis B vaccination measured through surveillance. Coverage levels for the third dose of hepatitis B vaccine (HepB3) should equal those of the third dose of pentavalent.

5.4.1 Routine Immunization

Universal Vaccination of Infants. High coverage with the primary vaccine series among infants aged < 12 months has the greatest overall impact on the prevalence of chronic HBV infection in children (*33*). As with other vaccines used in children aged less than 1 year, the aim of hepatitis B vaccination should be to reach at least 95% coverage in all municipalities (*41*, *42*).

This strategy offers the following significant advantages:

- Ease of integrating HBV vaccine into the existing immunization schedules in each country;
- Better compliance through the vaccination schedule for children aged less than 1 year;
- Possibility of combining vaccine antigens, as in DPT+HepB+Hib (pentavalent).

Booster injections after the infant schedule are usually not recommended because almost all children are protected following the primary vaccination schedule. Additionally, PAHO does not recommend routine postvaccination serologic testing (*42*).

Prevention of Perinatal Transmission. Hepatitis B vaccination at birth prevents perinatal transmission of HBV from HBsAg-positive mothers to their infants in > 90% of cases. The decision to add a birth dose should be based on the prevalence of carriers in the general population and the country's resources. PAHO recommends that the birth dose be added when seroprevalence is ≥ 8% (*42*). Only the monovalent hepatitis B vaccine should be used as the neonatal dose.

For schedule options that do and do not include the birth dose, refer to Chapter 7, Section 7.3.3 (Schedule and Dosage).

5.4.2 Other Vaccination Activities

Vaccination of Adolescents. Countries with intermediate or low hepatitis B endemicity may consider adding catch-up strategies targeted at older age groups such as adolescents with risk factors for acquiring HBV infection (*42*).

Vaccination of Health Care Workers and Other Groups at Risk. In addition to universal infant immunization, PAHO recommends vaccinating health care workers to protect them from hepatitis B as an occupational hazard and to reduce the risk of virus transmission from infected workers to patients in clinical settings (*42*).

Serology prior to vaccination to determine immune status is not indicated for health professionals.

Countries may also choose to vaccinate other groups with risk factors for acquiring HBV infection, such as patients who undergo hemodialysis, receive frequent transfusions, suffer chronic renal insufficiency, or who are infected with HIV; personnel and patients of institutions for the mentally disabled or drug addicts; homosexual and bisexual individuals; intravenous drug users; persons with multiple sex

partners or a history of sexually transmitted disease; individuals living with or having sexual contact with HBV carriers or those with acute infection; prisoners and prison personnel; and travelers to countries with high HBV endemicity.

5.4.3 Outbreak Control

In all hepatitis B outbreaks, epidemiological investigation should start rapidly with the aim of identifying the index case, his or her contacts, the mode of transmission, the population at greatest risk, and other significant factors. This is necessary in order to apply control measures and follow up on the cases, both clinically and in the laboratory. Existence of common sources of infection, such as a particular health facility, should be investigated so that necessary infection control steps can be taken.

5.4.4 Use of Hepatitis B Immune Globulin (HBIG)

The only available means of passive prevention of hepatitis due to HBV is the use of hepatitis B immune globulin (HBIG), which confers temporary immunity. Regular immune globulin has no impact on hepatitis B, since titers of anti-hepatitis B antibodies are usually low. Hepatitis B vaccine may be used in conjunction with HBIG, but they should be administered at different injection sites.

If HBIG is available in a particular country, its use is advisable in the following groups and situations:

- Newborns of HBsAg-positive mothers;
- Persons who have had percutaneous exposure or exposure of mucous membranes to blood contaminated by HBV; and
- Unimmunized sexual contacts of persons with acute, chronic HBV infection (with replication) (*35*).

The standard dose of HBIG is 0.5 mL for infants and 0.06 mL/kg for all other situations, administered intramuscularly.

Newborns of HBsAg-positive Mothers. In addition to hepatitis B vaccination, a dose of HBIG should be administered to newborns of HBsAG-positive mothers if HBIG is available in the country. HBIG (0.5 mL dose) should be given at birth or within the first 72 hours (although the effectiveness of the immune globulin beyond 12 hours from birth is not firmly established). This practice reduces by 70% the probability that the newborn will become a chronic carrier of HBV.

Breast milk does not pose any risk for HBV transmission for infants who have begun the vaccination series, whether or not they have received HBIG (*35*).

Percutaneous or Mucosal Exposure to HBsAg-positive Blood. For persons who have been exposed to HBV-contaminated blood, either percutaneously (needle prick, laceration, or bite) or through ocular or mucous membranes, the decision whether or not to administer HBIG prophylaxis should consider:

- Whether the source of the blood is known;
- The source's HBsAg levels; and
- Whether the exposed person has been vaccinated against HBV and, if so, his or her response to the vaccine.

Table 6 shows the recommendations used in the United States for prophylaxis against hepatitis B after percutaneous, ocular, or mucosal exposure to the virus, as an example. Countries should refer to their national recommendations, if available.

Sexual Exposure to an HBsAg-Positive Person. HBIG should be used as postexposure prophylaxis following sexual exposure to an infected person in addition to hepatitis B vaccination. HBIG given within seven days of exposure to an infected partner is about 75% effective in reducing acute hepatitis B disease and chronic infection.

Table 6. United States' recommendations for prophylaxis against hepatitis B after percutaneous, ocular, or mucosal exposure to the virus

	Treatment when the source is:		
Exposed person	**HBsAg-positive**	**HBsAg-negative**	**Unevaluated or unknown**
Unvaccinated or with incomplete vaccination series	HBIG[a] (one dose) and initiate or complete vaccination series	Initiate or complete vaccination series	HBIG and initiate or complete vaccination series
With complete vaccination series and:			
Protective levels of anti-HBs antibodies (≥10 mIU/mL)	None	None	None
Negative antibodies, non-respondent (<10 mIU/mL)	HBIG (one dose) and initiate reimmunization[b] or HBIG (two doses)	None	Treat as if the source were HBsAg-positive
Unknown antibody status	Carry out anti-HBs testing on the exposed individual[c] • If inadequate HBIG[a], one dose **and** vaccine booster dose[d] • If adequate, no treatment	None	Carry out anti-HBs testing on the exposed individual[c] • If inadequate, vaccine booster dose[d] • If adequate, no treatment

[a] Dose of hepatitis B immune globulin (HBIG), 0.06 mL/kg, intramuscularly.
[b] The option of giving one dose of HBIG (0.06 mL/kg) and reinitiating the vaccine series is preferred for nonresponders who have not completed a second three-dose vaccine series. For people who previously completed a second vaccine series but failed to respond, two doses of HBIG (0.06 mL/kg) are preferred: one dose as soon as possible after exposure and the second one month later.
[c] Adequate anti-HBs is ≥ 10mIU/mL.
[d] The person should be evaluated for antibody response after the vaccine booster dose. For persons who receive HBIG, anti-HBs testing should be performed when passively acquired antibody from HBIG is no longer detectable (e.g., four to six months); for persons who did not receive HBIG, anti-HBs testing should be done one to two months after the vaccine booster dose. If anti-HBs is inadequate (< 10 mIU/mL) after the vaccine booster dose, two additional doses should be administered to complete a three-dose reimmunization series.

Source: Adapted from American Academy of Pediatrics, Hepatitis B. In: Pickering LK, ed. *Red book: 2003 report of the Committee on Infectious Diseases*, 26th ed. Elk Grove Village, IL: American Academy of Pediatrics; ©2003:335, with permission.

Immunization services must take advantage of every opportunity to vaccinate persons who need to be immunized, particularly a parent or a child, either when someone visits a health facility for any type of care or when a person accompanies another to receive care.

6 EPIDEMIOLOGICAL SURVEILLANCE

6.1 GENERAL CONSIDERATIONS

Conducting adequate surveillance is a major component of the control strategies for all five diseases covered in this field guide. The impact of control strategies is measured by collecting surveillance data on disease incidence and vaccination coverage. Timely reporting allows for rapid investigation of cases of diphtheria, pertussis, Hib, and hepatitis B and satisfactory management of contacts. It also leads to early detection of outbreaks, which, in turn, allows for opportune implementation of outbreak control measures. For vaccines recently included in national immunization programs, such as Hib, trend analysis permits an assessment of the impact of vaccine introduction (*43*).

Specific actions and issues to be considered for the surveillance of the five diseases are outlined below.

Diphtheria

Critical activities for diphtheria surveillance in the Americas are:

- Routine case-based surveillance;
- Thorough case investigation; and
- Early investigation of outbreaks.

Pertussis

In the case of pertussis, routine surveillance can be case-based or consist of routine reporting of aggregated data from the local level to the central level, depending on the epidemiological situation and pentavalent coverage in each country. Sentinel surveillance to collect in-depth pertussis information, such as case-fatality rates by age groups, can be implemented in a few major hospitals; such surveillance should be linked to developments in laboratory diagnostics and networks.

Surveillance for parapertussis is not a priority at present.

Tetanus

Besides monitoring the occurrence of tetanus, tetanus (non-neonatal) surveillance should include assessment of the use of prophylaxis with adult-type diphtheria and tetanus toxoids (Td vaccine) and use of TIG in the routine management of wounds.

Haemophilus influenzae *type b (Hib)*

Even though Hib surveillance focuses mainly on Hib meningitis, including Hib in the surveillance for pneumococcus pneumonia is recommended due to the importance of Hib as an etiologic agent for pneumonia. In developing countries, Hib has been shown to be the cause of some 20% of pneumonias in children under 2 years old (*44*).

Epidemiological surveillance of pneumonias can be done through networks of sentinel hospitals, utilizing standardized radiological and clinical definitions. Countries may choose to incorporate other invasive Hib diseases (e.g., septic arthritis, epiglottitis) into their Hib surveillance programs, as necessary.

Hepatitis B

Routine surveillance of hepatitis B only considers acute disease; however, to fully understand the burden of hepatitis B, the sequelae of the disease such as chronic asymptomatic infections, cirrhosis, and primary cancer of the liver should also be considered. A report of low levels of acute viral hepatitis should not be misinterpreted as low incidence of HBV, as many of the infections occur asymptomatically. Data collection from other sources not routinely used, including hospital surveillance, mortality from hepatitis B complications, and cancer registries, may be necessary when assessing disease burden.

Besides vaccine coverage, assessing the seroprevalence of HBsAg in young children should assist in measuring the impact of hepatitis B vaccination (*42*).

Due to the characteristics and mode of transmission of hepatitis B, in addition to the general population, surveillance may also include: health workers in contact with blood samples and body fluids in the work environment; pregnant women; sex partners of carriers; blood recipients, such as hemophiliacs; employees of and persons confined to prisons, barracks, and psychiatric hospitals; and travelers to areas with high HBV prevalence.

6.2 CASE DEFINITIONS

Diphtheria

Clinical Description: A person of any age presenting laryngitis, pharyngitis, or tonsillitis, **and** an adherent membrane covering the tonsils, pharynx, and/or nasal septum.

Case Classification[a]

- *Suspected case:* Not applicable.
- *Probable case*: A case that meets the clinical description.
- *Confirmed case:* A probable case that has been laboratory-confirmed or epidemiologically linked to a laboratory-confirmed case.
- *Clinically confirmed case:* A probable case in which no other diagnosis has been laboratory-confirmed.

[a]Persons with positive *C. diphtheriae* cultures who do not meet the clinical description (i.e., asymptomatic carriers) should not be reported as probable or confirmed diphtheria cases.

Pertussis

Clinical Description: A case diagnosed by a health care worker, **or** a person presenting persistent cough for two or more weeks, without another apparent cause, **and** having at least one of the following manifestations:

- Paroxysms (i.e., fits) of coughing;
- Inspiratory "whooping"; and
- Post-tussive vomiting (i.e., vomiting immediately after coughing) without another apparent cause.

Case Classification:

- *Suspected case:* Not applicable.
- *Probable case:* A case that meets the clinical description.
- *Confirmed case:* A probable case that has been clinically confirmed where other causes have not been identified, laboratory-confirmed, or epidemiologically linked to a laboratory-confirmed case.
- *Laboratory-confirmed case:* A case from which *B. pertussis* has been isolated **or** with positive results by PCR.
- *Clinically confirmed case:* A probable case in which no other diagnosis has been confirmed.

Tetanus (non-neonatal tetanus)[b]

Clinical Definition: Tetanus is defined as the acute appearance of hypertonia or painful muscle contractions (usually in the neck or jaw) and generalized muscle spasms without another apparent medical cause.

- *Confirmed case:* A compatible clinical case reported by a health professional.

Haemophilus influenzae *type b (Hib)*

Hib surveillance should be integrated into meningitis surveillance. The definitions listed below should be used for the surveillance of Hib meningitis.

Case Classification:

- *Suspected case:* Every child aged 1 month to 5 years who presents clinical symptoms or signs of meningitis.
- *Probable case:* A suspected case whose cerebrospinal fluid (CSF) shows positive results with Gram's stain (Gram-negative coccobacillus for Hib) or shows at

[b]For neonatal tetanus case definitions please refer to Pan American Health Organization, *Neonatal Tetanus Elimination Field Guide* (Scientific and Technical Publication No. 602; Washington, D.C.: PAHO, 2005).

least one of the following alterations in cytochemistry suggestive of bacterial meningitis:

- Pleocytosis: white blood cell count ≥ 10 per mm^3, with a predominance of neutrophils;
- Low CSF glucose: glucose ≤ 50% of blood glucose;
- High CSF protein: proteins ≥ 45 mg/dL.

- *Confirmed case:* Every probable case with an isolation of *H. influenzae* type b from CSF or laboratory results indicating the presence of the bacteria by latex particle agglutination, immunoelectrophoresis, or PCR.

Additionally, Hib should be integrated into each country's existing local surveillance for pneumonia. As already mentioned, other forms of Hib invasive disease may be included in local Hib surveillance systems as national health authorities deem necessary.

Hepatitis B

Clinical Description: A person with jaundice who also presents choluria, acholic (clay-colored) stools, anorexia, asthenia, nausea, and liver enzyme levels 2.5 times higher than normal, without other attributable causes.

Case Classification:

- *Suspected case:* Not applicable.
- *Probable case:* A case that meets the clinical description.
- *Confirmed case:* A probable case confirmed by laboratory (compatible serology or histopathology).
- *Discarded case:* Laboratory results or clinical description not corresponding to the disease.
- *Carrier case:* An asymptomatic case who is HBsAg-positive six months after acquiring the infection.

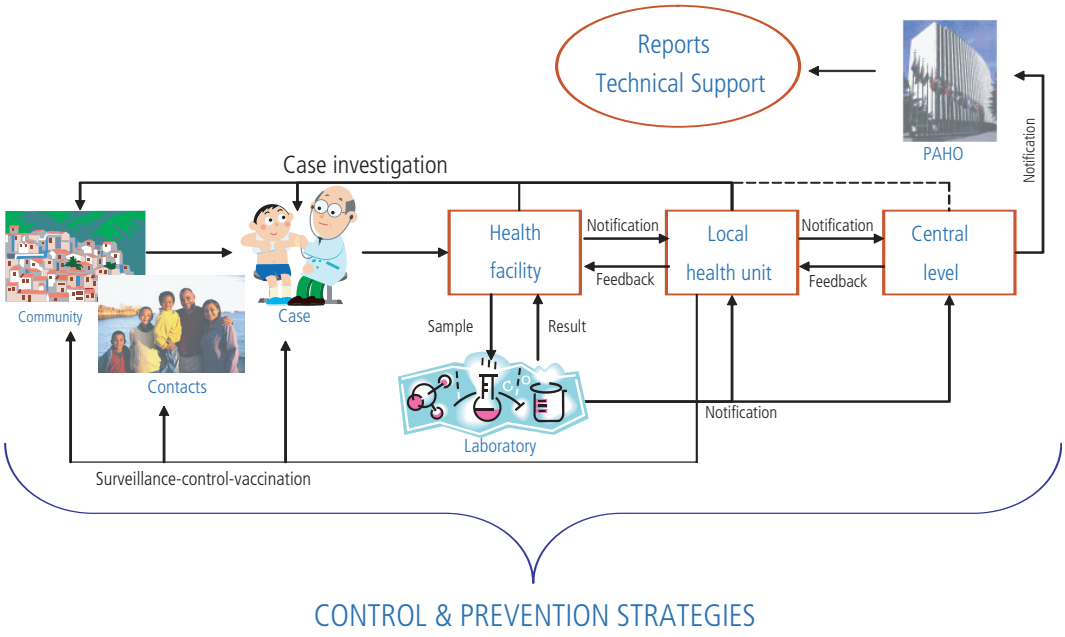
6.3 FLOW OF SURVEILLANCE INFORMATION

The flow of information and activities in the surveillance of vaccine-preventable disease is illustrated in Figure 15.

6.3.1 Case Reporting

Routine reporting is essential for the surveillance of most vaccine-preventable diseases. Public and private health practitioners should be aware of the characteristics and the occurrence of diphtheria, pertussis, tetanus (in addition to neonatal tetanus), Hib, and hepatitis B cases, and of the importance of reporting probable and confirmed cases through the routine surveillance system. Additionally, efforts

Figure 15. Vaccine-preventable disease surveillance flow.



should be made to ensure that laboratories conducting microbiological testing for *C. diphtheriae* and *B. pertussis* report cases to the health authorities. For hepatitis B, laboratories and blood banks should maintain a registry on positive tests for HBsAg and report at least monthly.

6.3.2 Case Investigation

Public health workers should investigate reports of probable cases of vaccine-preventable diseases to ensure that contacts are properly managed and that these diseases are adequately controlled. This is especially important when cases of diphtheria, pertussis, or Hib have been confirmed in institutions that cater to children, such as child-care centers, kindergartens, or schools. In addition to investigating cases and contacts, vaccination coverage should be evaluated at the municipality level in order to increase vaccination among those with low coverage.

For case-based surveillance, a unique identifier should be assigned to the person, and a case-investigation form should be used to obtain the following information: geographic location; age or date of birth; sex; immunization status and date of last dose of the specific vaccine; clinical history, including date of onset; laboratory results; treatment; outcome (recovery or death); information on contacts and their follow-up; and final classification of the case. Obtaining information on socioeconomic status may be useful to better guide control strategies. (See Annexes 2 to 7 for sample notification and investigation forms.)

6.3.3 Feedback

Feedback to health professionals participating in surveillance activities includes providing them with information on the number of cases reported by geographic area, a summary of the characteristics of the cases, information on the impact of control measures, and specific recommendations on how to improve case reporting. The results of analyses conducted at the national level should be shared periodically with the local health authorities and services. Feedback on surveillance can be given for several vaccine-preventable diseases at once, for example in the form of periodic bulletins.

6.4 DATA ANALYSIS AND SURVEILLANCE INDICATORS

6.4.1 Data Analysis

Table 7 summarizes the type of analysis suggested for diphtheria, pertussis, tetanus, Hib, and hepatitis B.

6.4.2 Surveillance Indicators

Indicators that can be used to monitor the surveillance system in general include:

- Number of health units notifying regularly;
- Proportion of cases reported on time (e.g., within 24 hours of diagnosis); and
- Proportion of cases adequately investigated.

Besides the indicators suggested above, the use of additional surveillance indicators depends on the local status of each particular disease. Suggested additional indicators for diphtheria, pertussis, and hepatitis B include:

Diphtheria

- Proportion of probable cases with nasopharyngeal or pharyngeal swab collected;
- Proportion of cases that are laboratory-confirmed; and
- Proportion of contacts managed properly.

Table 7. Data analysis for diphtheria, pertussis, tetanus, Hib, and hepatitis B

General[a]	Specific
• Incidence rates by geographic area • Specific incidence among vaccinated, unvaccinated, and incompletely vaccinated individuals • Age-specific incidence rates • Case-fatality rate and, if high, possible causes (e.g., poor case management, delays in starting specific treatment, patients not seeking care in time, etc.) • Coverage rates with the primary series (i.e., DTP3, Hib3, HepB3 or pentavalent-3 in children < 1 year) by municipality • Investigation of outbreaks in terms of person, place, and time (descriptive epidemiology), and determining risk factors for infection	**Tetanus[b]** • Local standards and practices used for wound management **Hib** • Proportion of bacterial meningitides caused by Hib • Proportion of consolidated pneumonias with isolation or diagnosis of Hib by laboratory **Hepatitis B** • Sex-specific incidence

[a] See glossary for explanation and calculation of rates.
[b] For specific neonatal tetanus data analysis and surveillance indicators refer to: Pan American Health Organization, *Neonatal tetanus elimination field guide*. Scientific and Technical Publication No. 602. Washington, D.C.: PAHO, 2005.

Pertussis (outbreaks)

- Proportion of outbreaks that are laboratory-confirmed; and
- Proportion of probable cases with nasopharyngeal aspirate or swab collected.

Hepatitis B

- Proportion of cases and/or outbreaks investigated;
- Proportion of contacts investigated; and
- Proportion of laboratories and blood banks that report monthly.

6.5 OUTBREAK RESPONSE

Outbreaks of vaccine-preventable diseases should be reported to the health authorities and investigated as soon as they come to the attention of the health system. Outbreak investigation increases understanding of the epidemiology of vaccine-preventable diseases and the reasons why the outbreak occurred (e.g., vaccine failure, failure to immunize, accumulation of susceptibles, waning immunity, and emergence of new toxigenic strains). Adequate outbreak investigation and response ensures the proper management of cases and contacts, and limits the spread of disease in the community.

Specific activities for outbreak control for each disease are addressed in Chapters 1 to 5.

7 VACCINES AGAINST DIPHTHERIA, PERTUSSIS, TETANUS, *HAEMOPHILUS INFLUENZAE* TYPE B, AND HEPATITIS B

7.1 DIPHTHERIA, PERTUSSIS, AND TETANUS VACCINES

7.1.1 Components

Vaccines against diphtheria, pertussis, and tetanus are commonly combined either as DPT, which contains diphtheria and tetanus toxoids and the whole-cell pertussis (wP) antigen, or as DTaP, which also contains diphtheria and tetanus toxoids, but has an acellular pertussis (aP) component with purified and inactivated components of *B. pertussis* cells. Diphtheria-tetanus vaccines not including the pertussis component are also available as DT for children and as Td, with a lower dose of diphtheria toxoid, for adults (*45*).

7.1.2 Immunity and Effectiveness

Diphtheria. After the administration of three doses of diphtheria toxoid, virtually all infants and adults develop diphtheria antibody titers greater than 0.01 IU/mL (the lowest level conferring some degree of protection). DTaP (diphtheria-tetanus-acellular pertussis) produces significantly lower geometric mean titers than DPT, but without clear clinical differences. Effectiveness seems to be 90% or higher for three or more doses and it has been seen that when diphtheria occurs in previously immunized persons, the disease tends to be less severe and has lower case-fatality rates.

Several serosurveys in Europe and the United States suggest a trend toward increasing susceptibility with advancing age, raising concerns regarding the duration of diphtheria toxoid-induced immunity. For this reason, most countries recommend periodical booster doses for adults with Td (tetanus-diphtheria for persons older than 7 years) (*45*).

Pertussis. There has been extensive experience with the use of wP vaccines. A primary series of four doses confers 70%–90% protection against serious pertussis disease. However, the immunity conferred by this vaccine wanes over time, and little or no protection is left 5–10 years after the last dose. The benefits of wP vaccine have been proven by the decline in morbidity and mortality from pertussis seen with the implementation of vaccination programs and the recurrence of disease when coverage levels have decreased (*45*).

Trials on aP vaccine have shown variable efficacies and it is not yet known if the duration of protection conferred by aP is comparable with wP vaccines. Some recent clinical trials comparing aP vaccine to wP vaccine have shown wP vaccine to be more effective, but the clinical significance of this finding is not clear (*45*).

In 2005, two aceullular pertussis vaccines for use in adolescents and adults were licensed in the United States. Both are formulated in **combination** with Td and contain a lower dose of the acellular pertussis component than the vaccines licensed and **used** for infants and children aged < 7 years.

PAHO's Technical Advisory Group (in 1997) and the World Health Organization (in its position paper of 1999 and 2005 update) recognized the effectiveness of whole cell pertussis (wP) vaccines in reducing the incidence of pertussis worldwide. The wP vaccines have a considerably lower price than acellular pertussis (aP) vaccines; where resources are limited and the vaccine is well accepted by the local population, wP remains the vaccine of choice. In countries where the higher reactogenicity of wP is an impediment to high vaccination coverage, aP may be used instead, at least for booster injections (*11*, *12*, *46*).

Tetanus. To provide active tetanus immunity, vaccines containing tetanus toxoid are used. Tetanus vaccine, when administered correctly and following the proposed schedule, is nearly 100% effective. Antitoxin levels higher than 0.01 IU/mL are considered protective. Protective antitoxin levels decrease over time, so a booster dose every 10 years is usually recommended.

7.1.3 Adverse Events and Contraindications

Diphtheria and tetanus toxoids

Diphtheria and tetanus toxoids are among the safest vaccines available. The reactions to vaccines containing diphtheria and tetanus toxoids can be classified as follows (*47*):

- **Local reactions:** erythema and induration with or without tenderness. These reactions are usually self-limited and require no therapy;
- **Exaggerated local (Arthus-like) reactions:** extensive, painful swelling, typically from shoulder to elbow, that usually begins two to eight hours after vaccination. These reactions are infrequent and more often reported in adults, particularly among those who have received frequent doses of diphtheria or tetanus toxoid;
- **Systemic reactions:** fever and malaise are rare; more severe anaphylactoid reactions have been reported on a few occasions.

The frequency and intensity of adverse reactions following vaccination with diphtheria and tetanus toxoids increase with the dose number and also vary with the prevaccination diphtheria-tetanus antitoxin levels.

Diphtheria-tetanus vaccine is contraindicated for those with severe allergic reactions to a vaccine component or a previous dose. Also, it is recommended to defer diphtheria and tetanus toxoid administration for persons experiencing moderate to

severe acute illness; those with mild illness may be vaccinated. Immunosuppression and pregnancy are **not** contraindications for using diphtheria-tetanus vaccines.

Pertussis vaccines

Pertussis vaccines are recognized for commonly causing local and systemic reactions. Most of these reactions, however, are mild, transient, and self-limited. Several events can occur within 48 hours after vaccination with a vaccine containing wP.

Though uncommon, reactions include seizures and what are known as hypotonic-hyporesponsive episodes. In rare cases, convulsions can occur with or without fever and are thought to be benign. There is no evidence that pertussis vaccines can induce epilepsy in children. A hypotonic-hyporesponsive episode is a shock-like state that occurs within 12 hours of vaccine administration, and although it may last a few hours, it always resolves. No causal link has been found between pertussis vaccines and permanent brain damage or death. Table 8 summarizes the range of adverse events attributed to vaccination with DPT.

Table 8. Adverse reactions attributable to vaccination with DPT

	Reactions per total number of doses
Local	
• Pain	1 per 2 doses
• Swelling	2 per 5 doses
• Redness	1 per 3 doses
Systemic	
• Fever ≥ 38°C	1 per 2 doses
• Fretfulness	1 per 2 doses
• Drowsiness	1 per 3 doses
• Anorexia	1 per 5 doses
• Vomiting	1 per 15 doses
• Persistent, inconsolable crying (i.e., for ≥ three hours)	1 per 100 doses
• Fever ≥ 40.5°C	1 per 330 doses
• Collapse (hypotonic-hyporesponsive episode)	1 per 1,750 doses
• Convulsions (with or without fever)[a]	1 per 1,750 doses

[a]The convulsions are chiefly febrile in origin, and the rate depends on the personal and family history and the age, with a lower risk in infants 4 months of age. Febrile convulsions are unlikely in children aged 6 years or older.
Source: Adapted from Cody CL, Baraff LJ, Cherry JD, Marcy SM, Manclark CR. Nature and rates or adverse reactions associated with DTP and DT immunizations in infants and children. *Pediatrics* ©1981;68(5):650–660, with permission from the American Academy of Pediatrics; and Pan American Health Organization. *Immunization safety. How to address events allegedly attributable to vaccination or immunization*. Washington, D.C.: PAHO, 2002.

Acellular pertussis (aP) vaccines are associated with a decreased rate of adverse events, especially those following the first four doses. However, an increase in the frequency and magnitude of local reactions after the fourth and fifth doses has also been seen with aP vaccines.

Most reactions following pertussis vaccination can be managed with acetaminophen or ibuprofen. Moreover, systematic administration of antipyretics at the time of vaccination and four to eight hours thereafter decreases the subsequent incidence of febrile and local reactions (*16*). Aspirin should not be used in children.

Absolute contraindications for pertussis vaccination include:

- A serious allergic reaction to a vaccine component or to a previous dose; and
- Encephalopathy within seven days of a prior vaccination, without another etiology.

Relative contraindications include the following reactions to a previous dose occurring within 48 hours of vaccination:

- Fever ≥ 40.5°C with no other cause;
- A hypotonic-hyporesponsive episode;
- Persistent, uncontrollable crying lasting more than three hours; and
- Convulsions, with or without fever, within three days of receiving a previous dose.

Precautions include moderate or severe acute illness. This prevents fever or other symptoms from being wrongly attributed to the vaccine.

Relative contraindications need to be weighed against the benefits in the event of an outbreak in the community. Pertussis vaccines are not recommended for children aged 7 years or older. Vaccine reactions are thought to be more frequent in older age groups and the burden of pertussis decreases with increasing age (*45*, *47*, *48*).

7.1.4 Schedule and Dosage

Three doses (the primary doses) of DPT given at least four weeks apart are needed to confer protection against diphtheria, tetanus, and pertussis. Booster doses, given no less than six months after the third dose and not before 1 year of age, may be necessary to maintain immunity.

In the Americas, all countries recommend that the three primary doses of DPT vaccine (or combination vaccines containing DPT) be given during the first year of life, usually at 2, 4, and 6 months, and most recommend at least one booster dose.

There is no need to restart the primary series, regardless of the time elapsed between doses. DPT vaccine is not recommended for children aged less than 6 weeks, for whom responses to pertussis are suboptimal.

When pediatric DT vaccine is used (in children aged less than 7 years for whom pertussis is contraindicated), the following schedule is recommended:

- Four doses should be used when the child has received the first dose before 12 months of age;
- Three doses—two doses of DT vaccine, given 2 months apart, and a third dose 6 to 12 months later—should be given for unimmunized children aged 1 to 7 years.

Unimmunized persons aged 7 years or older should receive a three-dose, adult Td vaccine series, with the second dose given 4 to 8 weeks after the first, and the third given 6 to 12 months later.

Booster doses with Td vaccine (for persons 7 years of age or older) to maintain immunity are suggested every 10 years. Td vaccinations fewer than 10 years apart are not recommended, as there are reports suggesting increased incidence and severity of adverse local reactions.

Patients recovering from tetanus disease should be vaccinated following the regular schedule for DPT or Td vaccine.

The standard pediatric dose of DPT and DT vaccines is 0.5 mL. DPT vaccine is usually purchased in multi-dose vials.

7.2 *HAEMOPHILUS INFLUENZAE* TYPE B VACCINES

Conjugate vaccines have proven to be an excellent tool to prevent the infections caused by *Haemophilus influenzae* type b. They consist of the capsular polysaccharide of the bacterium, linked to a protein carrier, which influences the immunological mechanism, transforming an antigen-independent T-cell response to an antigen-dependent T-cell response. Unlike the first vaccines developed for use against Hib, conjugate vaccines confer immunity in infants.

Three Hib conjugate vaccines[a] are authorized for use in infants and are interchangeable:

- HbOC (HibTITER®)
- PRP-OMP (PedvaxHIB®)
- PRP-T (ActHIB® and OmniHIB®).

A fourth Hib vaccine, PRP-D (ProHIBIT®), is only authorized for infants and children between 12 and 60 months of age and should not be used for the primary series.

Table 9. Conjugate vaccines against *Haemophilus influenzae* type b (Hib) and recommended vaccination series

Vaccine (brand)	Protein carrier	Usual schedule			
		2 months	4 months	6 months	12–15 months
HbOC (HibTITER®)	Mutant diphtheria toxin protein	First dose	Second dose	Third dose	Booster
PRP-T (ActHIB® or OmniHIB®)	Tetanus toxoid	First dose	Second dose	Third dose	Booster
PRP-OMP (PedvaxHIB®)	Outer meningococcus membrane B protein	First dose	Second dose		Booster
PRP-D (ProHIBIT®)	Diphtheria toxoid				Single dose or booster[a]

[a]PRP-D is authorized as a booster dose after a primary series of another type of vaccine for infants aged 12 months and as a single dose for infants who at 15 months of age have not been previously vaccinated.
Source: Adapted from Centers for Disease Control and Prevention, *Epidemiology and prevention of vaccine-preventable diseases*, Atkinson W, Hamborsky J, McIntyre L, Wolfe S, eds., 8th ed. Washington, D.C.: Public Health Foundation, 2005:101–113.

Table 9 shows the types of Hib conjugate vaccines available and their recommended vaccination series.

7.2.1 *Immunity and Effectiveness*

All three conjugate vaccines for use in infants are highly immunogenic. Effectiveness has been estimated at 95% to 100%. Invasive Hib disease in a fully vaccinated child is rare (*45*).

[a]HbOC refers to: oligosaccharides conjugated to diphtheria toxin protein; PRP-OMP refers to: polyribosylribitol phosphate polysaccharide conjugated to a meningococcal outer membrane protein; PRP-T refers to: polyribosylribitol phosphate polysaccharide conjugated to tetanus toxoid.

Hib vaccine is also immunogenic in patients with increased risk for invasive disease (patients with sickle-cell disease, leukemia or HIV infection). However, among HIV-infected persons, the immunogenicity varies with the degree of immunocompromise (*26*).

The effectiveness of Hib immunization is not only achieved by the direct protection provided by Hib vaccine, but also through an important herd effect due to a reduction in nasopharyngeal carriage of the microorganism in the population (*49*).

7.2.2 Adverse Events and Contraindications

Adverse events after vaccination with Hib conjugate vaccine are uncommon. Moderate fever tends to occur in 1 out of 20 vaccinated children. Edema, reddening, or pain at the injection site—or a combination of these—have been reported in one of every four cases. These symptoms usually resolve within 24 to 48 hours. Systemic reactions, such as high fever and irritability, are infrequent.

Vaccination with conjugate Hib is contraindicated for anyone who has experienced anaphylaxis following the administration of a previous dose of that vaccine.

7.2.3 Schedule and Dosage

All infants, including those born prematurely, should receive a primary series of Hib conjugate vaccine (separately or in a combination of vaccines) beginning at 2 months of age. Recent data indicate that if Hib conjugate vaccine is administered to infants aged less than 6 weeks, immunological tolerance to additional doses of Hib vaccine can be induced. Consequently, vaccines containing Hib conjugate should **not** be administered to children aged less than 6 weeks (*26*).

The number of doses in the primary series depends on the type of vaccine used. A primary series of the vaccine PRP-OMP (PedvaxHIB®) consists of two doses; HbOC (HibTITER®) and PRP-T (ActHIB® and OmniHIB®) require a primary series of three doses (see Table 9). Most countries in the Americas use the PRP-T vaccine.

A booster is sometimes administered at 12 to 15 months of age, regardless of which vaccine has been used for the primary series. Studies are being conducted in four Latin American countries to evaluate differences in vaccination effectiveness, if any, between three-dose schedules with a booster and without a booster dose.

The optimal interval between doses is two months; the minimum interval between them is one month. The booster dose, if used, should be given at least two months after the previous dose.

Infants and children unvaccinated at 7 months of age or older may not require a series totaling three or four doses. The number of doses that an infant needs in order to complete the series depends mainly on his or her age at the time of consultation.

Important issues regarding Hib conjugate vaccines (*26*):

- The three Hib conjugate vaccines authorized for use in infants are interchangeable.
- A series that includes vaccines of more than one type will still induce a level of protective antibodies.
- If it is necessary to change the type of vaccine, **three** doses of **any** combination constitute the primary series.
- Any authorized conjugate vaccine may be used for the booster dose, regardless of the type used in the primary series.

Children between 15 and 60 months of age who have not received a previous dose of any Hib conjugate vaccine should receive a single dose. In general, children over 60 months do not need to be vaccinated.

The Hib conjugate vaccine PRP-OMP is available in combination with hepatitis B vaccine (Comvax®). In addition, PRP-T (ActHIB®) is available in combination with DTaP in a product called TriHIBit®. However, TriHIBit® is authorized for use only as the fourth dose of the Hib and DTaP series due to reduced immunogenicity of the Hib component when used as a combination. Thus, TriHIBit® should not take the place of the first, second, or third dose of the Hib series (*26*).

The standard pediatric dose is 0.5 mL; Hib conjugate vaccines are available in liquid or lyophilized (freeze-dried powder) form, in single- or multi-dose vials. They can be utilized as monovalent vaccines or in combination with other vaccines, such as DPT and/or the hepatitis B vaccine (see Section 7.4 on combination vaccines in this chapter).

7.3 HEPATITIS B VACCINES

The hepatitis B vaccine used in the Americas is an inactivated recombinant vaccine obtained through genetic engineering. This vaccine contains the subunit of the surface antigen (HBsAg) obtained from purified hepatitis B virus (HBV) through the recombinant DNA (rDNA) technique in *Saccharomyces cerevisiae* yeasts, in which the gene responsible for the synthesis of the HBsAg (S gene) is inserted. These recombinant vaccines are interchangeable.

7.3.1 Immunity and Effectiveness

Three doses of vaccine are required to induce an adequate response of protective antibodies (anti-HBs ≥ 10 milli-IU/mL in more than 90% of healthy adults and more than 95% of children and adolescents). Protective titers begin to be reached two weeks after the second dose, and the effectiveness of the vaccine is 95%–98%. The

third dose confers optimal protection, acting as a booster dose. In a three-dose schedule, longer intervals between the last two doses (4–12 months) result in higher final titers of anti-HBs (*50*, *51*). Several studies have shown that the currently licensed vaccines produce high rates of seroconversion (>95%) and induce adequate levels of anti-HBs when administered to infants at birth, 2 months, and 6 months of age, or at 2, 4, and 6 months of age (*52*).

Some factors that influence seroconversion after a complete vaccination series are:

- Age: Individuals aged more than 40 years present a smaller proportion of seroconversion;
- Type of host: Immunocompromised patients, such as those with chronic renal insufficiency, those infected by HIV, and those being treated with immunosuppressors, have a lower percentage of seroconversion (50%–70%);
- Application site: Application in the gluteal region yields lower levels of seroconversion in adults due to decreased absorption of the immunizing antigen in that area.

There is disagreement about whether smoking, male sex, obesity, and diabetes mellitus influence seroconversion. Some 10% of adults are considered non-responders: that is, they do not present an antibody response to the initial vaccination series.

Studies indicate that the duration of immunity as measured by serology varies. However, long-term studies in children and adults indicate that immunological memory remains intact after up to 15 years of monitoring and that the antibodies protect against chronic HBV infection, although the concentrations of anti-HBs may be low or undetectable (*35*).

7.3.2 Adverse Events and Contraindications

Hepatitis B vaccine is a safe vaccine, although it does produce some local effects in 3%–9% of vaccinees, such as pain, erythema, and induration, which are generally transitory. These reactions are more common in adults (13%–29%).

Some systemic symptoms, which are slight and transitory, have been reported: fatigue, headache, and irritability in 8% to 18% of vaccinated children, and fever above 37.7°C in 0.4% to 8% of children. These reactions disappear spontaneously in a few days, and do not require interruption of the vaccination schedule.

Hepatitis B vaccine does not produce adverse effects in chronic carriers. Individuals who have had an unrecognized past infection with positive anti-HBsAg and receive hepatitis B vaccine are not at greater risk of adverse reactions.

Recombinant DNA hepatitis B vaccine cannot transmit HBV or any other virus (e.g., HIV) because the vaccine is produced through genetic engineering.

Prior anaphylaxis due to any component of this vaccine is a contraindication for its use. However, it can be administered without risk to pregnant women, since it contains noninfectious particles of HBsAg.

7.3.3 Schedule and Dosage

Three-dose schedules for hepatitis B vaccine, not including the birth dose, usually follow the DPT schedule and are given as pentavalent at 2, 4, and 6 months of age.

As mentioned in Chapter 5, some countries with high prevalence of hepatitis B infection will choose to include a dose of hepatitis B vaccine at birth to prevent perinatal transmission. Whether or not the birth dose is used in a particular country, there are several options for including hepatitis B vaccine in the immunization schedule for children aged < 1 year.

Some countries that administer the birth dose of hepatitis B and have the pentavalent vaccine in their schedule, utilize the following schedule: monovalent hepatitis B (is administered) at birth, followed by three doses of pentavalent, usually at 2, 4, and 6 months. These countries find this approach to be programmatically easier and administer four doses of hepatitis B antigen.

Others countries that use three-dose schedules of hepatitis B antigen, including a birth dose, usually follow the schedule used for children born to HBsAg-positive mothers, that is:

- First dose at birth (within 24 hours of birth);
- Second dose at 1–2 months of age; and
- Third dose at 6 months.

In this series, the last two doses are usually administered simultaneously with DPT and Hib vaccines.

In general, a minimum interval of four weeks is recommended between the first and second doses of hepatitis B vaccine, and eight weeks between the second and third. Studies have shown that longer intervals between the last two doses may increase the final anti-HBs titers but do not affect seroconversion rates (*52*).

Hepatitis B vaccine is presented in mono-dose or in multiple-dose vials that contain 2, 6, or 10 doses of vaccine. They contain aluminum hydroxide as adjuvant and often thimerosal as preservative. Each dose of lyophilized vaccine contains 5, 10, or 20 µg of antigen (HBsAg), reconstituted in 0.5 or 1 mL doses, according to the manufacturer's instructions. Table 10 summarizes the number of doses and the antigen concentration recommended for different groups.

Table 10. Doses of hepatitis B vaccine recommended, according to age and type of person

Type of person	Number of doses [a]	Antigen concentration [b]
Newborns, infants, and persons aged less than 20 years	Three doses	5 or 10 µg
Premature infants with birthweight < 2,000 grams	Four doses [c]	5 or 10 µg
Persons 20 years of age or older	Three doses	10 or 20 µg
Immunocompromised individuals, including HIV-positive cases, and hemodialysis patients	Three to four doses	40 µg

[a] Not all available hepatitis B formulations should be used in infants < 6 weeks of age. Always read the vaccine package insert.
[b] Doses (antigen concentration) vary depending on the manufacturer.
[c] For infants who weighed less than 2,000 g at birth, the initial vaccine dose should not be counted toward completion of the hepatitis B series, and 3 additional doses of hepatitis B vaccine should be administered beginning when the infant is 1 month of age.
Sources: Mast E, Mahoney F, Kane MA, Margolis HS. Hepatitis B Vaccine. *In:* Plotkin SA, Orenstein WA, eds. *Vaccines*, 4th ed. Philadelphia: W.B. Saunders, Co.; 2004:314, with permission from Elsevier; Centers for Disease Control and Prevention. *Epidemiology and prevention of vaccine-preventable diseases*, Atkinson W, Hamborsky J, McIntyre L, Wolfe S, eds., 8th ed., Washington, D.C.: Public Health Foundation, 2005:200.

7.4 COMBINATION VACCINES

A combination vaccine consists of two or more antigens physically combined in a single preparation. Currently, numerous combination vaccines have been developed and are available on the market, but only a few are routinely used in the Americas.

PAHO recommends that countries use combination vaccines in their routine immunization schedule (*53*). Combination vaccines have several advantages for children and their parents, clinicians, and for health services at all levels. The main advantages of combination vaccines include:

- Reduced number of injections, which in turn reduces the risk of injection complications and discomfort to infants;
- Lower costs and simplified logistics for the health system;
- Fewer missed vaccination opportunities; and
- Better acceptance by parents and health care workers.

In addition, experience from the Americas suggests that hepatitis B3 coverage is usually lower than the coverage for DPT3 in countries that use the monovalent hepatitis B vaccine (*42*).

7.4.1 Available Combinations

In this section, we present only some of the combinations available in the Region, excluding combinations with inactivated poliovirus (IPV) and acellular pertussis. However, we acknowledge that countries may decide to use other combination vaccines in their immunization schedules or as new combinations become available.

DPT+Hib+Hep B (Pentavalent). The use of a combination vaccine against diphtheria, tetanus, pertussis, Hib, and hepatitis B, known as pentavalent vaccine, is widespread in Latin America. The immunogenicity and safety profile is the same as for DPT+Hep B.

DPT+Hib. Several studies have evaluated the immunogenicity and safety of combining DPT with Hib conjugate vaccines. Even though some studies have shown a reduced response to the Hib component, as measured by mean PRP antibody levels, the levels are still high and the reduction appears to have no clinical importance. This has been further suggested by studies showing protection against disease in populations using DPT+Hib combinations. Although a slight increase in adverse events has been seen with DPT+Hib compared with DPT alone, the combination vaccines using DPT and any of the Hib formulations show less adverse reaction than the aggregate of local reactions seen when separate vaccines are given in different injection sites (*45*).

DPT+Hep B. The combination of DPT with Hep B has shown immune responses comparable to those obtained when the vaccines are given separately, as well as comparable adverse events.

Table 11 summarizes the formulation of selected combination vaccines.

The contraindications and precautions for the use of combined vaccines are the same as those of the individual components (i.e., DPT, Hib, and hepatitis B vaccines). Vaccination should be delayed in infants and children with moderate or serious acute disease. Milder illnesses, such as mild upper respiratory tract infections, are not contraindications for vaccination.

For the pentavalent vaccine, the diphtheria, tetanus, pertussis, and hepatitis B components are presented as a suspension in saline solution in a glass vial or pre-filled syringe, and the Hib component is a white pellet that comes in a separate vial (see Annex 8).

Table 11. Formulations of selected combination vaccines available in the Americas

Vaccine	Formulation of each 0.5 mL dose[a]				
	Diphtheria toxoid	Tetanus toxoid	Pertussis vaccine	Hib	Hep B
DPT/Hib	30 IU	60 IU	2–4 IU	10 µg PRP conjugated to 25 µg of cross-reactive mutant	—
DPT/Hep B	30 IU	60 IU	4 IU	—	10 µg HBsAg
DPT/Hib/Hep B	30 IU	60 IU	4 IU	10 µg PRP conjugated to tetanus	10 µg HBsAg
Hib/Hep B	—	—	—	7.5 µg PRP	5 µg HBsAg

[a] Formulations may vary by manufacturer.

Source: Adapted from Decker MD, Bogaert HH, Combination vaccines. *In:* Plotkin SA, Orenstein WA, eds. *Vaccines*, 4th ed. 827–830. ©2004, Philadelphia: W.B. Saunders Co, with permission from Elsevier.

Credit: Ingrid Valenzuela, Social Communicator for Immunization Programs, Guatemala.

Figure 16. Proper final disposal of syringes and needles in "sharp boxes."

7.5 COLD CHAIN, STORAGE, AND SAFE INJECTION PRACTICES

DPT vaccine should be stored at a temperature between 2°C and 8°C and should not be frozen, to avoid reducing its potency. Of the DPT components, pertussis antigen is the most susceptible to temperature. The other vaccines (hepatitis B and Hib) should be transported and stored at temperatures between 2°C and 8°C and should not be frozen, except lyophilized Hib, which is not affected by freezing. As for the other vaccines, other cold chain requirements, such as using refrigerators designated exclusively for vaccines, need to be addressed.

For all injectable vaccines, injection safety should be ensured, including the adequate use of safety boxes ("sharps boxes") for used syringes and needles and their proper final disposal (see Figure 16).

7.6 VACCINE ADMINISTRATION

Diphtheria, tetanus, pertussis, Hib, and hepatitis B vaccines can be administered either simultaneously in different injection sites (if not combined), or at any time before or after injection of other inactivated or live vaccines.

Pentavalent, DPT, DTaP, DT, Td, hepatitis B, and other combination vaccines are administered intramuscularly:

- For infants and young children, the preferred injection site is the vastus lateralis muscle in the anterolateral aspect of the middle or upper thigh using a 23–25 gauge, 7/8-inch to 1-inch needle.
- For older children (usually 36 months and older) and adults, the preferred site is the thickest portion of deltoid muscle, below the acromion, using a 23–25 gauge, 1-inch to 2-inch needle.

The injection of these vaccines in the gluteal area can be dangerous in small children and result in reduced immunogenicity, especially for the Hep B component.

Hib vaccines may be injected subcutaneously, but if Hib is given with other antigens, it should be used intramuscularly. Nevertheless, subcutaneous injection may be considered for patients with thrombocytopenia or bleeding disorders.

It is important to highlight that combination vaccines requiring reconstitution of the lyophilized Hib component should be reconstituted with the DPT+Hep B vaccine produced by the same manufacturer. The entire content of the diluent vial, whether using Hib vaccine alone or the combination with DPT or DPT+Hep B liquid vaccine,

should be added to the vial containing the lyophilized Hib vaccine; the vial must then be shaken until the pellet is completely dissolved (see Annex 8).

When using multidose vials, each dose should be withdrawn with a sterile needle and under strict aseptic conditions to avoid contaminating the vial.

7.7 FINAL CONSIDERATIONS

When planning to introduce Hib and/or hepatitis B vaccine into an immunization program, it is important to consider the vaccine formulation (combination vs. monovalent) and presentation (1- vs. 10-dose vials). The formulation and presentation selected will help determine the expense, wastage percentage, cold chain space, need for reconstitution, and training activities for health care workers.

Sustaining vaccination activities against diphtheria, pertussis, tetanus, Hib, and hepatitis B, and striving to reach vaccination coverage levels of 95% or more in each municipality, are critical for keeping these diseases under control in the Americas.

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ANNEXES

ANNEX 1. Summary of the epidemiological characteristics of diphtheria, pertussis, tetanus, *Haemophilus influenzae* type b, and hepatitis B

	Diphtheria	Pertussis	Tetanus	Hib	Hepatitis B
Infectious agent	Toxigenic strains of *Corynebacterium diphtheriae*	*Bordetella pertussis*	*Clostridium tetani*	*Haemophilus influenzae* type b	Hepatitis B virus DNA virus of the Hepadnaviridae family
Reservoir	Human carriers are the reservoir for *C. diphtheriae*	Humans	Intestines of horses and other animals, including humans Soil or fomites **contaminated** with feces containing the spores of *C. tetani*	Humans	Humans
Occurrence	Worldwide. Most frequent in colder months in temperate zones	Worldwide. Most common in young children	Worldwide	Worldwide: Mainly affects children aged 2 to 3 years	Worldwide with few seasonal variations
Transmission	Person-to-person from the respiratory tract of a case or from transient carriers. Rarely from fomites or skin lesions	Person-to-person via aerosolized droplets produced from a cough or sneeze or by direct contact with secretions from the respiratory tract of infectious individuals	Spores contained in soil and feces are usually introduced to the body through wounds and less frequently after surgical procedures, including circumcision	Person-to-person from the respiratory tract via aerosolized droplets	Through body fluids: blood, saliva, semen, etc. Sexual contact, household contact, perinatal exposure, intravenous drug use, and nosocomial exposure
Incubation period	Two to five days (range: 1–10 days)	7–20 days (range: 4–21 days)	Eight days (range: 3–21 days)	Unknown due to high rate of asymptomatic carriage (probably two to four days)	60–90 days (range: six weeks to six months)
Communicability	Transmission can occur as long as the toxigenic bacteria are present in discharges and lesions (normally ≤ two weeks and seldom more than four weeks). Antibiotic therapy terminates shedding. Rare chronic carriers shed the bacilli for six months or more	Pertussis cases are most infectious during the catarrhal period and the first two weeks after cough onset; some individuals may be infectious for a longer period. Antibiotic treatment reduces the period of communicability	Not contagious as it is not transmitted from person-to-person	While the bacteria remains in the respiratory tract. Antibiotic treatment reduces the period of communicability	All persons who are HBsAg positive. From weeks before onset through the acute phase. The infectivity of chronically infected persons varies
Immunity	- Some protection from maternal antibodies in infants < six months - Following disease or asymptomatic infection (at least partial) - Long-lasting protection after three doses of toxoid (no protection against colonization)	- Maternal protection of infants has not been demonstrated - Vaccine-induced immunity may wane	- Does not necessarily result from disease (immunization is indicated for cases) - For at least 10 years following immunization with tetanus toxoid - Infants of actively immunized mothers	- Some protection from maternal antibodies and breast-feeding until 2 months of age - Following Hib infection and possibly some cross-reactions to other organisms - Following vaccination	- Long-lasting protection through disease or vaccination

Sources: Centers for Disease Control and Prevention (CDC). *Epidemiology and prevention of vaccine-preventable diseases.* (Atkinson W, Hamborsky J, McIntyre L, Wolfe S, eds.), 8th ed. Washington, D.C.: Public Health Foundation, 2005; Heymann DL, ed., *Control of communicable diseases manual,* 18th ed. Washington, D.C.: American Public Health Association; 2004, reprinted with permission from the American Public Health Association.

ANNEX 2. Example of Diphtheria Notification and Investigation Form

[Name of institution]

Notification and Investigation form – DIPHTHERIA

Case number			
State/Province		District	
Municipality		Neighborhood/Landmarks	
Informant		Telephone	
Service			

I. CASE IDENTIFICATION

First and last name					
Address					
Telephone					
Mother's name		Father's name			
Sex	☐ Male ☐ Female	Date of birth	Day	Month	Year
If date of birth unavailable, age	Years _____	Months _____	Days _____		

II. BACKGROUND

Date of symptom onset	Day	Month	Year	Consultation date	Day	Month	Year
Notification date	Day	Month	Year	Investigation date	Day	Month	Year
Case identified by:	☐ Spontaneous consultation (passive)			☐ Institutional search	☐ Community search		
Contact with confirmed case	☐ Yes ☐ No ☐ Unk			Attendance at school, kindergarten, or day care	☐ Yes ☐ No ☐ Unk		
Number of diphtheria vaccine doses	☐ 0 ☐ 1 ☐ 2 ☐ ≥ 3 ☐ Unknown			Date of last dose	Day	Month	Year
Type of vaccine:	☐ DTP ☐ Pentavalent ☐ Other_____			Vaccination information obtained by:	☐ Vaccination card ☐ Health services ☐ Parents or another adult		

III. CLINICAL DATA, FOLLOW-UP AND TREATMENT

Signs and symptoms		**Complications**	
Fever (grade _____)	☐ Yes ☐ No ☐ Unk	Neurological	☐ Yes ☐ No ☐ Unk
Tonsillitis	☐ Yes ☐ No ☐ Unk	Cardiac	☐ Yes ☐ No ☐ Unk
Pharyngitis	☐ Yes ☐ No ☐ Unk	Renal	☐ Yes ☐ No ☐ Unk
Laryngitis	☐ Yes ☐ No ☐ Unk	Tracheotomy	☐ Yes ☐ No ☐ Unk
Membranes (where _____)	☐ Yes ☐ No ☐ Unk	Other complications	☐ Yes ☐ No ☐ Unk
Thoracic retraction	☐ Yes ☐ No ☐ Unk	Other symptoms and complications:	

Hospitalization	☐ Yes ☐ No ☐ Unk	Admission date	Day	Month	Year
Name of hospital		Registry/history #			
Final status	☐ Recovered ☐ Transferred to _____ ☐ Dead ☐ Unknown	Date of discharge/death	Day	Month	Year

Antibiotics	☐ Yes ☐ No ☐ Unk	Type of antibiotics			
Duration of antibiotic therapy (days)		Date of last antibiotic dose	Day	Month	Year
Antitoxin	☐ Yes ☐ No ☐ Unk				
Dose of antitoxin		Date of antitoxin	Day	Month	Year
Other treatment:					

IV. SAMPLES AND LABORATORY ANALYSIS

	SAMPLE 1			SAMPLE 2			SAMPLE 3			SAMPLE 4		
Type of sample	☐ Nasopharyngeal ☐ Membrane ☐ Serum ☐ Other: _____			☐ Nasopharyngeal ☐ Membrane ☐ Serum ☐ Other: _____			☐ Nasopharyngeal ☐ Membrane ☐ Serum ☐ Other: _____			☐ Nasopharyngeal ☐ Membrane ☐ Serum ☐ Other: _____		
Identification #												
Date taken	Day	Month	Year	Day	Month	Year	Day	Month	Year	Day	Month	Year
Date sent												
FOR LABORATORY USE												
Date received	Day	Month	Year	Day	Month	Year	Day	Month	Year	Day	Month	Year
Laboratory name												
Identification # in laboratory												
Type of test												
Results	☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed			☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed			☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed			☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed		
If *C. diphtheriae* was isolated, toxigenicity	☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed			☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed			☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed			☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed		
Result dates	Day	Month	Year	Day	Month	Year	Day	Month	Year	Day	Month	Year

V. CLASSIFICATION

			Day	Month	Year
Final classification	☐ Laboratory confirmation ☐ Confirmed by epidemiological association ☐ Probable ☐ Discarded, final diagnosis: _____	Date classified			
Classified by (Name)					

Investigator		Telephone	
Institution			
Signature		Date	

Observations: _____

ANNEX 3. Example of a form for the management of contacts*

Date of investigation:_____ Person in charge of investigation: _____ ID: _____

Contact	Type of contact (Ex. father, mother, children)	Age		Sex (M/F)	Vaccination status		Symptoms	Management of contacts						Comments
		Years	Months		# Doses	Source of information		Vaccination		Result of culture	Antibiotic		Other medication	
								Vaccine	Date		Type	Date		
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														

Socioeconomic characteristics of the family

# of persons in household:	Adults	Children	Position of the case in the family:		Schooling:	Father	Mother	# of rooms (used for sleeping):	
Floor: ☐ Cement ☐ Soil ☐ Other			Water source: ☐ Inside the house ☐ Outside			Excretal disposal: ☐ Flush toilet ☐ Latrine ☐ Open field			
Trade/profession of the father			Trade/profession of the mother			Family monthly income			

*All persons of any age who live under the same roof as the case and, if the child goes to school, his/her classmates are considered at risk. In very crowded areas also consider close neighbors as contacts.

ANNEX 4. Example of Pertussis-like Illness Notification and Investigation Form

[Name of institution] **Notification and Investigation form – PERTUSSIS-LIKE ILLNESS**

Case number			
State/Province		District	
Municipality		Neighborhood/Landmarks	
Informant		Telephone	
Service			

I. CASE IDENTIFICATION

First and last name					
Address					
Telephone					
Mother's name		Father's name			
Sex	☐ Male ☐ Female	Date of birth	Day	Month	Year
If date of birth unavailable, age	Years _____	Months _____	Days _____		

II. BACKGROUND

Date of symptom onset	Day	Month	Year	Consultation date	Day	Month	Year
Notification date	Day	Month	Year	Investigation date	Day	Month	Year
Case identified by:	☐ Spontaneous consultation (passive)			☐ Institutional search	☐ Community search		
Contact with confirmed case	☐ Yes ☐ No ☐ Unk			Attendance at school, kindergarten, or day care	☐ Yes ☐ No ☐ Unk		
Number of pertussis vaccine doses	☐ 0 ☐ 1 ☐ 2 ☐ ≥3 ☐ Unknown			Date of last dose	Day	Month	Year
Type of vaccine:	☐ DTP ☐ Pentavalent ☐ Other_____			Vaccination information obtained by:	☐ Vaccination card ☐ Health services ☐ Parents or another adult		

III. CLINICAL DATA, FOLLOW-UP AND TREATMENT

Signs and symptoms		**Complications**	
Cough Duration _____ days	☐ Yes ☐ No ☐ Unk	Post-tussive vomiting (vomiting after coughing)	☐ Yes ☐ No ☐ Unk
Paroxysmal cough episodes	☐ Yes ☐ No ☐ Unk	Cyanosis	☐ Yes ☐ No ☐ Unk
Inspiratory whoop	☐ Yes ☐ No ☐ Unk	Unconsciousness	☐ Yes ☐ No ☐ Unk
Other symptoms and complications:			

Hospitalization	☐ Yes ☐ No ☐ Unk	Admission date	Day	Month	Year
Name of hospital		Registry/history #			
Final status	☐ Recovered ☐ Transferred to _____ ☐ Dead ☐ Unknown	Date of discharge/death	Day	Month	Year

Antibiotics	☐ Yes ☐ No ☐ Unk	Type of antibiotics			
Duration of antibiotic therapy (days)		Date of last antibiotic dose	Day	Month	Year
Antitoxin	☐ Yes ☐ No ☐ Unk				
Other treatment:					

IV. SAMPLES AND LABORATORY ANALYSIS

	SAMPLE 1			SAMPLE 2			SAMPLE 3			SAMPLE 4		
Type of sample	☐ Nasopharyngeal aspirate ☐ Nasopharyngeal swab ☐ Other: _____			☐ Nasopharyngeal aspirate ☐ Nasopharyngeal swab ☐ Other: _____			☐ Nasopharyngeal aspirate ☐ Nasopharyngeal swab ☐ Other: _____			☐ Nasopharyngeal aspirate ☐ Nasopharyngeal swab ☐ Other: _____		
Identification #												
Date taken	Day	Month	Year	Day	Month	Year	Day	Month	Year	Day	Month	Year
Date sent												
FOR LABORATORY USE												
Date received	Day	Month	Year	Day	Month	Year	Day	Month	Year	Day	Month	Year
Laboratory name												
Identification # in laboratory												
Type of test												
Results	☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed			☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed			☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed			☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed		
Result dates	Day	Month	Year	Day	Month	Year	Day	Month	Year	Day	Month	Year

V. CLASSIFICATION

			Day	Month	Year
Final classification	☐ Laboratory confirmation ☐ Confirmed by epidemiological link ☐ Probable ☐ Discarded, final diagnosis: _____	Date classified			
Classified by (Name)					

Investigator		Telephone	
Institution			
Signature		Date	

Observations: _____

ANNEX 5. Example of Tetanus Notification and Investigation Form

[Name of institution] **Notification and Investigation form – TETANUS (Not neonatal)**

Case number			
State/Province		District	
Municipality		Neighborhood/Landmarks	
Informant		Telephone	
Service			

I. CASE IDENTIFICATION

First and last name					
Address					
Telephone					
Mother's name		Father's name			
Sex	☐ Male ☐ Female	Date of birth	Day	Month	Year
If date of birth unavailable, age	Years _____	Months _____	Days _____		

II. BACKGROUND

Date of symptom onset	Day	Month	Year	Consultation date	Day	Month	Year
Notification date	Day	Month	Year	Investigation date	Day	Month	Year
Wound present:	☐ Yes ☐ No ☐ Unk			Date of wound occurrence	Day	Month	Year
Anatomic site and description of wound							
Number of tetanus vaccine doses	☐ 0 ☐ 1 ☐ 2 ☐ ≥3 ☐ Unknown			Date of last dose	Day	Month	Year
Type of vaccine:	☐ DTP ☐ Pentavalent ☐ Other_____			Vaccination information obtained by:	☐ Vaccination card ☐ Health services ☐ Parents or another adult		

III. CLINICAL DATA, FOLLOW-UP AND TREATMENT

Signs and symptoms		**Complications**	
Trismus ("lockjaw")	☐ Yes ☐ No ☐ Unk	Opisthotonos	☐ Yes ☐ No ☐ Unk
Difficulty swallowing	☐ Yes ☐ No ☐ Unk	Abdominal rigidity	☐ Yes ☐ No ☐ Unk
Muscle spasms	☐ Yes ☐ No ☐ Unk	Other symptoms	☐ Yes ☐ No ☐ Unk
Clinical type	☐ Generalized ☐ Cephalic ☐ Localized ☐ Unknown	Other symptoms and complications:	

Hospitalization	☐ Yes ☐ No ☐ Unk	Admission date	Day	Month	Year
Name of hospital		Registry/history #			
Final status	☐ Recovered ☐ Transferred to _____ ☐ Dead ☐ Unknown	Date of discharge/death	Day	Month	Year

Tetanus immunoglobulin	☐ Yes ☐ No ☐ Unk				
Dose of TIG		Date of last TIG dose	Day	Month	Year
Other treatment:					

V. CLASSIFICATION

			Day	Month	Year
Final classification	☐ Confirmed ☐ Discarded, final diagnosis: _____	Date classified			
Classified by (Name)					

Investigator		Telephone	
Institution			
Signature		Date	

Observations: ----------

ANNEX 6. Example of *Haemophilus influenzae* type b Meningitis Notification and Investigation Form

[Name of institution]

Notification and Investigation form – *HAEMOPHILUS INFLUENZAE* TYPE B (Hib) MENINGITIS

Case number			
State/Province		District	
Municipality		Neighborhood/Landmarks	
Informant		Telephone	
Service			

I. CASE IDENTIFICATION

First and last name					
Address					
Telephone					
Mother's name		Father's name			
Sex	☐ Male ☐ Female	Date of birth	Day	Month	Year
If date of birth unavailable, age	Years _____	Months _____	Days _____		

II. BACKGROUND

Date of symptom onset	Day	Month	Year	Consultation date	Day	Month	Year
Notification date	Day	Month	Year	Investigation date	Day	Month	Year
Case identified by:	☐ Spontaneous consultation (passive)			☐ Institutional search	☐ Community search		
Contact with confirmed case	☐ Yes ☐ No ☐ Unk			Attendance at school, kindergarten, or day care	☐ Yes ☐ No ☐ Unk		
Number of Hib vaccine doses	☐ 0 ☐ 1 ☐ 2 ☐ ≥3 ☐ Unknown			Date of last dose	Day	Month	Year
Type of vaccine:	☐ DTP+Hep B ☐ Pentavalent ☐ Hib+Hep B ☐ Other _____			Vaccination information obtained by:	☐ Vaccination card ☐ Health services ☐ Parents or another adult		

III. CLINICAL DATA, FOLLOW-UP AND TREATMENT

Signs and symptoms		**Complications**	
Fever (grade _____)	☐ Yes ☐ No ☐ Unk	Vomiting	☐ Yes ☐ No ☐ Unk
Stiff neck	☐ Yes ☐ No ☐ Unk	Lethargy	☐ Yes ☐ No ☐ Unk
Bulging fontanelle (infant)	☐ Yes ☐ No ☐ Unk	Irritability or alteration of mental alertness, stupor, or coma	☐ Yes ☐ No ☐ Unk
Difficulties suckling (infant)	☐ Yes ☐ No ☐ Unk	Convulsions (fits)	☐ Yes ☐ No ☐ Unk
Petechial rash	☐ Yes ☐ No ☐ Unk	Other meningeal signs	
Other complications or sequelae	☐ Hearing loss ☐ Visual impairment ☐ Motor alterations ☐ Other _____		

Hospitalization	☐ Yes ☐ No ☐ Unk	Admission date	Day	Month	Year
Name of hospital		Registry/history #			
Final status	☐ Recovered ☐ Transferred to _____ ☐ Dead ☐ Unknown	Date of discharge/death	Day	Month	Year

Antibiotics	☐ Yes ☐ No ☐ Unk	Type of antibiotics			
Duration of antibiotic therapy (days)		Date of last antibiotic dose	Day	Month	Year
Other treatment:					

IV. SAMPLES AND LABORATORY ANALYSIS

	SAMPLE 1			SAMPLE 2			SAMPLE 3			SAMPLE 4		
Type of sample	☐ Cerebrospinal fluid (CSF) ☐ Other: _____			☐ Cerebrospinal fluid (CSF) ☐ Other: _____			☐ Cerebrospinal fluid (CSF) ☐ Other: _____			☐ Cerebrospinal fluid (CSF) ☐ Other: _____		
Identification #												
Date taken	Day	Month	Year	Day	Month	Year	Day	Month	Year	Day	Month	Year
Date sent												
FOR LABORATORY USE												
Date received	Day	Month	Year	Day	Month	Year	Day	Month	Year	Day	Month	Year
Laboratory name												
Identification # in laboratory												
Type of test												
Results	☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed			☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed			☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed			☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed		
Result dates	Day	Month	Year	Day	Month	Year	Day	Month	Year	Day	Month	Year
Serotype result	☐ _____ ☐ Undetermined ☐ Not processed			☐ _____ ☐ Undetermined ☐ Not processed			☐ _____ ☐ Undetermined ☐ Not processed			☐ _____ ☐ Undetermined ☐ Not processed		
Result dates	Day	Month	Year	Day	Month	Year	Day	Month	Year	Day	Month	Year

V. CLASSIFICATION

			Day	Month	Year
Final classification	☐ Suspected ☐ Laboratory confirmation ☐ Probable ☐ Discarded, final diagnosis: _____	Date classified			
Classified by (Name)					

Investigator		Telephone	
Institution			
Signature		Date	

Observations: _____

ANNEX 7. Example of Hepatitis B Notification and Investigation Form

[Name of institution] **Notification and Investigation form – HEPATITIS B**

Case number			
State/Province		District	
Municipality		Neighborhood/Landmarks	
Informant		Telephone	
Service			

I. CASE IDENTIFICATION

First and last name					
Address					
Telephone					
If patient under 18 yrs, Mother's name		If patient under 18 yrs, Father's name			
Sex	☐ Male ☐ Female	Date of birth	Day	Month	Year
If date of birth unavailable, age	Years _____	Months _____	Days _____		

II. BACKGROUND

Date of symptom onset	Day	Month	Year	Consultation date	Day	Month	Year
Notification date	Day	Month	Year	Investigation date	Day	Month	Year
Case identified by:	☐ Spontaneous consultation (passive)			☐ Institutional search	☐ Community search		
Born to carrier mother	☐ Yes ☐ No ☐ Unk			Place of birth of the case (city/province/country)			
Household or other contact of a probable/confirmed Hep B case	☐ Yes ☐ No ☐ Unk			If yes, specify contact	☐ Household ☐ Sexual partner ☐ Other		
Recipient of blood (or blood products)	☐ Yes ☐ No ☐ Unk			Date of transfusion(s)	Day	Month	Year
Has undergone hemodialysis	☐ Yes ☐ No ☐ Unk			Is/was health care worker	☐ Yes ☐ No ☐ Unk		
Has used IV drugs	☐ Yes ☐ No ☐ Unk			Has been institutionalized	☐ Yes ☐ No ☐ Unk		
Other known risk factors							
Number of hepatitis B vaccine doses	☐ 0 ☐ 1 ☐ 2 ☐ ≥3 ☐ Unknown			Date of last dose	Day	Month	Year
Type of vaccine:	☐ DTP+Hep B ☐ Pentavalent ☐ Hib+Hep B ☐ Other _____			Vaccination information obtained by:	☐ Vaccination card ☐ Health services ☐ Parents or another adult		

III. CLINICAL DATA, FOLLOW-UP AND TREATMENT

Signs and symptoms		**Complications**	
Jaundice	☐ Yes ☐ No ☐ Unk	Nausea/vomiting	☐ Yes ☐ No ☐ Unk
Abdominal pain	☐ Yes ☐ No ☐ Unk	Fatigue	☐ Yes ☐ No ☐ Unk
Anorexia	☐ Yes ☐ No ☐ Unk	Fulminant hepatitis	☐ Yes ☐ No ☐ Unk
Other symptoms and complications:			

Hospitalization	☐ Yes ☐ No ☐ Unk	Admission date	Day	Month	Year
Name of hospital		Registry/history #			
Final status	☐ Recovered ☐ Transferred to _____ ☐ Dead ☐ Unknown	Date of discharge/death	Day	Month	Year

Prior use of Hep B immunoglobulin	☐ Yes ☐ No ☐ Unk	If yes, specify:
Treatment:		

IV. BLOOD SAMPLES AND LABORATORY ANALYSIS

	SAMPLE 1			SAMPLE 2			SAMPLE 3			SAMPLE 4		
Identification #												
Date taken	Day	Month	Year	Day	Month	Year	Day	Month	Year	Day	Month	Year
Date sent												
FOR LABORATORY USE												
Date received	Day	Month	Year	Day	Month	Year	Day	Month	Year	Day	Month	Year
Laboratory name												
Identification # in laboratory												
RESULTS HBsAg ☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed	Anti-HBs ☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed			Anti-HBc ☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed			Anti-HBcAg ☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed			HBeAg ☐ Positive ☐ Negative ☐ Undetermined ☐ Not processed		
Result dates	Day	Month	Year	Day	Month	Year	Day	Month	Year	Day	Month	Year

V. CLASSIFICATION

			Day	Month	Year
Final classification	☐ Confirmed ☐ Probable ☐ Discarded, final diagnosis: _____	Date classified			
Classified by (Name)					

Investigator		Telephone	
Institution			
Signature		Date	

Observations: ----------

ANNEX 8. How to reconstitute and administer lyophilized DTP+Hib+ Hepatitis B (pentavalent) vaccine

IMPORTANT FACTS TO CONSIDER

Lyophilized Hib+DTP+hepatitis B vaccine comes in two separate vials:
- One vial contains liquid DTP + hepatitis B vaccine (used as a diluent)
- The second vial contains a lyophilized (freeze-dried) Hib vaccine

- Only use the DPT-Hep B vaccine supplied with the lyophilized Hib vaccine
- Never use water or any other diluent to reconstitute the pentavalent vaccine
- Remember that the diluent IS the DTP-Hep B component of the vaccine

RECONSTITUTING

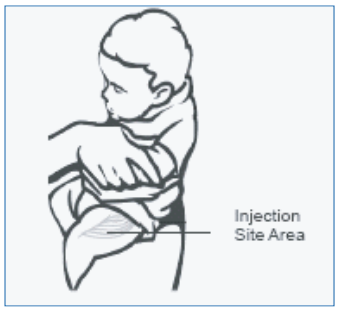
- Make sure you have both vials and 2 mL mixing (reconstitution) syringes
- Check the expiry date of the DTP + hepatitis B vaccine:
  - Discard vaccine that is too old or has been exposed to too much heat
- Use the shake test to determine if the DTP + hepatitis B vaccine has been frozen:
  - Do not use DTP + hepatitis B vaccine that has been frozen, or that you suspect has been frozen.
- Using the mixing syringe, draw up all of the DTP + hepatitis B vaccine (used as diluent). Inject it into the vial containing the lyophilized Hib vaccine.
- Remove the mixing syringe from the vaccine vial and shake the vial, or roll it between your palms, until the powder is fully dissolved and there are no visible particles in the vial.

IMPORTANT: Discard any reconstituted pentavalent vaccine after six hours, or at the end of each session, whichever comes first

ADMINISTERING

- Use a 0.5 mL syringe and needle (disposable or auto-disable), the same type of syringe and needle as are routinely used for DTP injections
- Draw 0.5 mL of reconstituted (mixed) vaccine into the injection syringe
- Administer as an intramuscular injection (IM) in the infant's outer mid-thigh*:

*NEVER give intramuscular injections in the buttock of infants as there is risk of damaging nerves in that area. Also, it will result in a reduction in immunogenicity, especially for the Hep B component of the vaccine.



NOTE: A sterile syringe and needle must be used for each injection and discarded in a safety box. The syringe and needle used for reconstitution should not be used for giving the injection

REMEMBER THE FOLLOWING PRECAUTIONS

To facilitate the adequate reconstitution of the pentavalent vaccine, always:
- Log the vaccines AND diluents in the stock inventory books
- Avoid keeping the lyophilized Hib vaccine and the DTP-Hep B vaccine (used as diluent) separated

During supervisory visits, supervisors must ensure the proper reconstitution and administration of the pentavalent vaccine by:
- Observing the reconstitution and injection process
- Ensuring the availability of the same number of lyophilized Hib and DTP-Hep B vials

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Source: PATH (*Program for Appropriate Technology in Health*). Immunizing children against *Haemophilus influenzae* type b (Hib). A training module for vaccinators. Available at http://www.childrensvaccine.org/html/ip_clinical.htm#training

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