Chapter 4

Communicable Diseases

INTRODUCTION

Despite advances in medical sciences and public health, infectious diseases remain a central task of public health in the twenty-first century, especially HIV/AIDS, TB, malaria, SARS, avian flu, and others. Globalization has facilitated the spread of many infectious agents to all corners of the globe. Mass travel, economic globalization, and climate changes along with accelerating urbanization of human populations are causing environmental disruption, including global warming. There are and will be more consequences in international transmission of infectious diseases than are now known, in humans and wildlife.

This chapter describes communicable diseases and programs for their prevention, control, elimination, and eradication. Control of communicable disease requires a systems approach using available resources effectively, mobilizing environmental measures, immunization, and clinical and

health systems. Rapid transportation and communication make a virus outbreak in any part of the world an international concern, both for professionals and the general public. A basic understanding of infectious diseases is therefore an expectation of any student, just as a general knowledge of family health, chronic disease, nutrition, and economics are part of the modern public health culture.

The material presented in this chapter is intended to give an introduction for the student or review for the public health practitioner, with an emphasis on the applied aspects of communicable disease control. We have relied for the content of this chapter on several standard references, especially Heymann's *Control of Communicable Diseases Manual,* 18th ed. *WHO Vaccine Preventable Diseases Monitoring System: 2007 Global Summary*; *Jawetz, Melnick and Adelberg's Medical Microbiology,* 21st ed., along with *Morbidity and Mortality Weekly Report* of the Centers for Disease Control and Prevention (CDC), and WHO's Weekly Epidemiologic Record (WER). ProMed is a highly recommended Harvard University–based Web site, frequent update source of current infectious disease outbreaks around the world, available with free subscription at Web site listed in electronic resources.We also have relied on electronic sources such as PubMed, the American Academy of Pediatrics, World Health Organization (WHO), and United Nations Children's Fund (UNICEF) Web sites, as well as library access journals. The references listed will augment the limited discussion possible in this text.

PUBLIC HEALTH AND THE CONTROL OF COMMUNICABLE DISEASE

Organized public health grew out of the sanitation movement of the mid-nineteenth century which sought to reduce the environmental and social factors in communicable disease (Box 4.1). Traditionally, the prevention and control of communicable diseases has been accomplished by sanitation, safe water and food supply, isolation, and immunization.

Box 4.1 Communicable Disease

A communicable disease "is an illness due to a specific infectious agent or its toxic products that arises through transmission of that agent or its products from an infected person, animal, or inanimate reservoir to a susceptible host." Transmission may be direct from person to person, or indirect through an intermediate plant or animal host, vector, or the inanimate environment.

Source: Heymann, D. L. (ed.) 2004. *Control of Communicable Diseases Manual,* 18th ed. Washington, DC: American Public Health Association.

The potential for infectious disease to disturb or destroy human life still exists and may increase as infectious diseases evolve and escape current man-made control mechanisms. The spread of plague throughout Europe and Asia in the fourteenth century and subsequent pandemics of smallpox, tuberculosis, syphilis, measles, cholera, and influenza show the explosive potential and epidemic nature of infectious diseases. The spread of AIDS since the 1980s; ongoing cholera epidemics in Asia, Africa, and South America; and diphtheria in the former Soviet Union in the 1990s, remind us why communicable disease control is still one of the major responsibilities of public health.

Both the miasma (environment–host) and bacteriologic (agent–host) theories contributed to great achievements in the control of communicable disease in the first half of the twentieth century. The emergence of the germ theory in the late nineteenth century led to the sciences of bacteriology and immunology, growing out of the work of Jenner, Pasteur, Koch, Lister, and many others (see Chapter 1). The control of the vaccine-preventable diseases has been a boon to humankind, saving countless millions of lives and providing a cornerstone for public health. Despite this, millions of children still die annually from preventable diseases. Infectious diseases of childhood are still tragically undercontrolled internationally. Infectious diseases also undermine the health of other vulnerable groups in the population, such as the elderly and the chronically ill, thereby playing a major role in the economics of health care.

Great strides have been made in the control of communicable diseases through environmental sanitation, safe foods, vaccination, and antibiotics, as seen in Figure 4.1, in the United States and equally in the other industrialized countries. However, the field of infectious disease continues to be dynamic and challenging. Emerging infectious disease threats from new diseases not previously identified, such as HIV and SARS, or new variants of old diseases with resistance to current methods of treatment together provide great challenges to public health. Increasing resistance to therapeutic agents augments the need for new strategies and coordination between public health and clinical services. Understanding the principles and methods of communicable disease control and eradication is important for all health providers and public health personnel.

THE NATURE OF COMMUNICABLE DISEASE

An infectious disease may or may not be clinically manifest so that a person may carry the disease agent without having clinical illness. Acute infectious diseases are intense or short-term, but may have long-term sequelae of great public health importance, such as post-streptococcal glomerulonephritis or rheumatic heart disease. Other infectious diseases are chronic with their own long-term

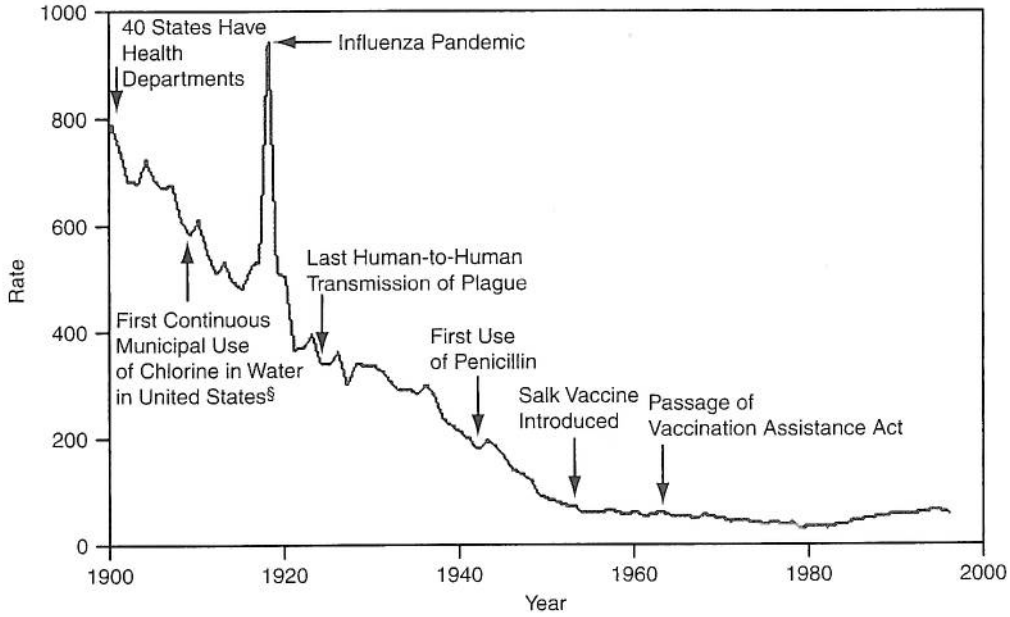


FIGURE 4.1 Crude death rate from infectious diseases – United States 1900–1999. Source: Centers for Disease Control. 1999. Achievements in Public Health, 1900–1999: Control of Infectious Diseases. *Morbidity and Mortality Weekly Report*, 48:621–629.

effects, such as HIV infection or peptic ulcers. Infections may have both short-term and long-term morbidity, as with viral hepatitis infections. The stages of infectious disease include:

1. Exposure and infection;
2. Presymptomatic/prodromal stage;
3. Nonmanifested or subclinical disease;
4. Clinically manifested disease and its progression;
5. Resolution, recovery, remission, relapse, suprainfection, or death; and
6. Long-term sequelae.

Each disease has its own characteristic organism and natural history from onset to resolution. Many infectious diseases may remain at a presymptomatic or subclinical stage without progressing to clinical symptoms and signs, but may be transmissible to other persons. Even a subclinical disease may cause an immunologic effect, producing immunity. The drama of infectious disease is exemplified in the tragic event of the plague in the fourteenth century and its periodic recurrence as in the epidemic of 1665 in London, described by Daniel Defoe (Box 4.2).

Box 4.2 Daniel Defoe—A Journal of the Plague Year, London, 1665

"It was about the beginning of September 1664, that I, among the rest of my neighbors, heard, in ordinary discourse that the plague had returned again in Holland; for it had been very violent there, and particularly in Amsterdam and Rotterdam, in the year 1663, whither they say, it was brought, some said from Italy, others from the Levant, among some goods, which were brought home by their Turkey fleet; others said it was brought from Candia; others from Cyprus. It mattered not from whence it came; but all agreed it was come into Holland again.

"It was now mid-July and the plague, which had chiefly raged at the other end of town ... began to now come eastwards toward the part where I lived. It was to be observed, indeed, that it did not come straight on toward us; for the city, that is to say within the walls, was indifferently healthy still; nor was it got over the water into Southwark; for though there died that week 1,268 of all distempers, whereof it might be supposed above 900 died of the plague, yet there was but 28 in Southwark, Lambeth parish included; whereas in the parishes of St. Giles and St. Martin-in-the-Fields alone there died 421."

Source: Defoe, D. 1723. A *Journal of the Plague Year*. Winnipeg: Meridian Classic, 1984, reprint.

HOST–AGENT–ENVIRONMENT TRIAD

The host–agent–environment triad, discussed in Chapter 2, is fundamental to the success of understanding transmission of infectious diseases and their control, including those well known, those changing their patterns, and those newly emerging or escaping current methods of control. Infection occurs when the organism successfully invades the host's body, where it multiplies and produces an illness.

A host is a person or other living animal, including birds and arthropods, who provides a place for growth and sustenance to an infectious agent under natural conditions. Some organisms, such as protozoa or helminths, may pass successive stages of their life cycle in different hosts, but the definitive host is the one in which the organism passes its sexual stage. The intermediate host is where the parasite passes the larval or asexual stage. A transport host is a carrier in which the organism remains alive, but does not develop.

An agent of an infectious disease is necessary, but not always sufficient to cause a disease or disorder. The infective dose is the quantity of the organism needed to cause clinical disease. A disease may have a single agent as a cause, or it may occur as a result of the agent in company with contributory factors, whose presence is also essential for the development of the disease. A disease may be present in an infected person in a dormant form such as tuberculosis, or a subclinical stage such as poliomyelitis or HIV, without clinical paralytic disease in the case of polio or before clinical AIDS appears in the case of HIV. The virulence or pathogenicity of an infective agent is the capacity of an infectious agent to enter the host, replicate, damage tissue, and cause disease. Virulence describes severity of clinical disease and may vary among serotypes or strains of the same agent.

The environment provides a reservoir for the organism and the mode of transmission by which the organism reaches a new host. The reservoir is the natural habitat where an infectious agent lives and multiplies, from which it can be transmitted directly or indirectly to a new host. Reservoirs may be in people, animals, arthropods, plants, soil, or substances in which an organism normally lives and multiplies, and on which it depends for survival or in which it survives in a dormant form. A fomite is an inanimate object contaminated with infectious material which may transmit disease, such as improperly sanitized medical equipment.

Contacts are persons or animals who have been in association with an infected person, animal, fomite, or environment that might provide a risk for acquiring the infective agent. Persons or animals that harbor a specific infectious agent, often in the absence of discernible clinical disease, and who serve as a source of infection or contamination of food, water, or other materials, are carriers. A carrier may have an unapparent infection (a healthy carrier) or may be in the incubation or convalescent stage of the infection.

CLASSIFICATIONS OF COMMUNICABLE DISEASES

Communicable diseases may be classified by a variety of methods: by clinical syndrome, mode of transmission, methods of prevention (e.g., vaccine-preventable), or by major organism classification; that is, viral, bacterial, fungal, and parasitic disease.

A virus is a nucleic acid molecule (RNA or DNA) encapsulated in a protein coat or capsid. The virus is not a complete cell and can only replicate inside a living cell. The capsid may have a protective lipid-containing envelope. The capsid and envelope facilitate attachment and penetration into host cells, and often contain virulence factors. Inside the host cell, the nucleic acid molecule utilizes cellular proteins and processes for virus replication. Prions — discovered in recent years (Stanley Prusiner, Nobel Prize, 1997) — are proteins, which in a properly folded state, induce disease. As infectious agents, prions cause a number of degenerative central nervous system diseases, including spongiform encephalopathy in livestock (mad cow disease and scrapie) and humans (variant Creutzfeldt-Jakob disease).

Bacteria are unicellular organisms that reproduce sexually or asexually and can exist in an environment with oxygen (aerobic) or in a situation lacking oxygen (anaerobic). Some may enter a dormant state and form spores where they are protected from the environment and may remain viable for years. Bacteria include a nucleus of chromosomal DNA material within a membrane surrounded by cytoplasm, itself usually enclosed by a cellular membrane. Bacteria are classified by morphology and growth conditions, including coloration under Gram stain (gram-negative or gram-positive), microscopic morphology, immunologic (antigen) or molecular (DNA) markers, or by the diseases they may cause. Bacteria include both indigenous flora (normal resident) bacteria and pathogenic (disease-causing) bacteria. Pathogenic bacteria cause disease by invading, overcoming natural or acquired resistance, and multiplying in the body. Bacteria may produce a toxin or poison that can affect a body site distant from where the bacterial replication occurs, such as in tetanus. Bacteria may also initiate an excessive immune response, producing damage to other body tissues away from the site of infection (e.g., acute rheumatic fever and glomerulonephritis).

Mycoses are infections caused by molds and yeasts. Clinical manifestations of fungal disease range from relatively mild superficial infection to systemic, life-threatening conditions. Immunocompromised individuals are at elevated risk. *Cryptococcus, Candida, Aspergillus*, and *Mucor* molds are among the leading causes of morbidity in HIV disease and among immunosuppressed populations. *Pneumocystis jiroveci* (formerly *P. carinii*), once thought to be a protozoan, is now classified a fungus, based on genetic analysis. Common dermatophytic infections, known as tinea, are caused by fungi invading the hair, skin, or nails, and occur in nearly all living organisms.

Parasitology studies protozoa, helminths, and arthropods that live within, on, or at the expense of a host. Protozoa include oxygen-producing, unicellular organisms such as the flagellates *Giardia* and *Trichomonas*, and amoebae such as *Entamoeba*, in enteric and gynecologic

disorders. Sporozoa are parasites with complex life cycles in different hosts, such as cryptosporidium or malarial parasites. Helminths are worms that infest humans, especially in poor sanitation and tropical areas. Arthropods, the most numerous of animal species, include lice, fleas, sandflies, blackflies, and ticks, are important disease vectors. They can live at the body's surface (ectoparasites) and transmit bacterial, viral, rickettsial, or other diseases, or by oral–fecal transmission, such as *Shigella* and *E. coli*, in or via biological effects within the host such as in malaria. This group constitutes one of the most important public health threats globally and their control is a continuing challenge for public health.

MODES OF TRANSMISSION OF DISEASE

Transmission of diseases is by the spread of an infectious agent from a source or reservoir to a person (Table 4.1). Direct transmission from one host to another occurs during touching; biting; kissing; sexual intercourse; projection via droplets, as in sneezing, coughing, or spitting; or by entry through the skin. Indirect transmission includes via aerosols of long-lasting suspended particles in air and fecal–oral transmission such as food- and waterborne as well as by poor hygienic conditions with fomites, such as soiled clothes, handkerchiefs, toys, or other objects. Transmission in medical settings is common and preventable by hand washing and sterile techniques.

Vector-borne diseases are transmitted via crawling or flying insects, in some cases with multiplication and development of the organism in the vector, as in malaria.

The subsequent transmission to humans is by injection of salivary gland fluid during biting or by deposition of feces, urine, or other material capable of penetrating the skin through a bite wound or other trauma. Transmission may occur with insects as a transport mechanism, as in *Shigella* on the legs of a housefly.

Airborne transmission occurs indirectly via infective organisms in small aerosols that may remain suspended for long periods of time and which easily enter the respiratory tract. This occurs frequently with viruses such as influenza, the common cold, and measles. Particles of dust may spread organisms from soil, clothing, or bedding.

Vertical transmission occurs from one generation to another or from one stage of the insect life cycle to another stage. Maternal–infant transmission occurs during pregnancy (transplacental), delivery (as in gonorrhea), or breastfeeding (e.g., HIV, with transfer of infectious agents from mother to fetus or newborn).

IMMUNITY

Resistance to infectious diseases is related to many host and environmental factors, including age, sex, pregnancy, nutrition, trauma, fatigue, living and socioeconomic conditions, and emotional status. Good nutritional status has a protective effect and bolsters immunocompetence. Vitamin A supplements reduce complication rates of measles and enteric infections. Tuberculosis may be present in an individual whose resistance is sufficient to prevent clinical disease, but the infected person is a carrier of an organism which can be transmitted to another or cause clinical disease if the person's susceptibility is reduced (Box 4.3).

Immunity is resistance to infection resulting from presence of specific antibodies and complement proteins or cells that act on the microorganism associated with a

TABLE 4.1 Classification of Infectious Diseases by Principal Modes of Transmission

Mode	Method	Examples
Direct	Airborne (droplet and aerosols)	Viral exanthems (measles), streptococcal diseases, various upper and lower respiratory tract diseases, tuberculosis, Legionnaire's disease, influenza
Direct	Physical contact	Leprosy, impetigo, scabies, anthrax
Direct	Sexual contact	HIV, syphilis, gonorrhea, herpes genitalis, hepatitis B, chlamydia, human papillomavirus
Indirect	Blood and blood products	HIV, hepatitis B, hepatitis C
Indirect	Oral-fecal Hygiene Food-borne Water-borne	Cholera, *Shigella*, *Salmonella*, typhoid, botulism, *Campylobacter*, *Staphylococcus aureus*, cryptosporidium, *Listeria*, worms, *Giardia*, hepatitis A, rotavirus, enteroviruses, poliovirus, adenoviruses, *Entamoeba histolytica*
Indirect	Transcutaneous	Vector-borne via insects (arthropod): malaria, viral hemorrhagic fevers, schistosomiasis, plague Animal bite (zoonoses): rabies Health care (iatrogenic): hospital infections, HIV, hepatitis B Self-injected (illicit drug users): HIV, hepatitis B
Vertical	Congenital Maternal-fetal	Congenital rubella syndrome, congenital syphilis, gonorrheal ophthalmia, cytomegalovirus (CMV) HIV, rubella, syphilis, hepatitis B, gonorrhea, chlamydia

Box 4.3 Basic Terms in Immunology of Infectious Diseases

Infectious agent a pathogenic organism (e.g., virus, bacteria, rickettsia, fungus, protozoa, or helminth) capable of producing infection or an infectious disease.

Infection the process of entry, development, and proliferation of an infectious agent in the body tissue of a living organism (human, animal, or plant) overcoming body defense mechanisms, resulting in an inapparent or clinically manifest disease.

Antigen a substance (e.g., protein, polysaccharide) capable of inducing specific response mechanisms in the body. An antigen may be introduced into the body by invasion of an infectious agent, by immunization, inhalation, ingestion, or through the skin, wounds, or via transplantation.

Antibody a protein molecule formed by the body in response to a foreign substance (an antigen) or acquired by passive transfer. Antibodies bind to the specific antigen that elicits its production, causing the infective agent to be susceptible to immune defense mechanisms against infections (e.g., humoral and cellular).

Immunoglobulins antibodies that meet different types of antigenic challenges. They are present in blood or other body fluids, and can cross from a mother to fetus *in utero*, providing protection during part of the first year of life. There are five major classes (IgG, IgM, IgA, IgD, and IgE) and subclasses based on molecular weight.

Antisera or antitoxin materials prepared in animals for use in passive immunization against infection or toxins.

Source: Brooks, G. E., Butel, J. S., Morse, S. A. 2004 *Jawetz, Melnick and Adelberg's Medical Microbiology*, 23rd ed. Stamford, CT: Appleton & Lange.

specific disease or toxin. Immunity can be acquired by response to an organism or its antigenic components in the body of a person having the infective organism, producing natural immunity, or by immunization. In active immunization, the body responds to introduced antigens by producing antibodies. Passive immunity is temporary, by the passage of preformed antibody from mother to infant in breast milk or injection of preformed immunoglobulins. The body also reacts to infective antigens by cellular responses, including those that directly defend against invading organisms and other cells which produce antibodies.

The immune response is the resistance of a body to specific infectious organisms or their toxins provided by a complex interaction including:

Humoral

a. B cells (bone marrow and spleen) produce antibodies which circulate in the blood.
b. Complement proteins, a humoral response which causes lysis of foreign cells.

Cell Mediated

c. T cell immunity is provided by sensitization of lymphocytes of thymus origin to mature into cytotoxic cells capable of destroying virus-infected or foreign cells.
d. Phagocytosis, a cellular mechanism which ingests microorganisms (macrophages and neutrophils).

SURVEILLANCE

Surveillance of disease is the continuous scrutiny of all aspects of occurrence and spread of disease pertinent to effective control of that disease. Maintaining ongoing surveillance is one of the basic duties of a public health system, and is vital to the control of communicable disease, providing the essential data for tracking of disease, planning interventions, and responding to future disease challenges. Surveillance of infectious disease incidence relies on reports of notifiable diseases by physicians, supplemented by individual and summary reports of public health laboratories. Such a system must concern itself with the completeness and quality of reporting and potential errors and artifacts. Quality is maintained by seeking clinical and laboratory support to confirm first reports. Completeness, rapidity, and quality of reporting by physicians and laboratories should be emphasized in undergraduate and postgraduate medical education. Enforcement of legal sanctions may be needed where standards are not met. Surveillance of infectious diseases includes the following:

1. Morbidity reports from clinics to public health offices;
2. Mortality reports from attending doctors to vital records;
3. Reports from selected sentinel centers, e.g., emergency rooms, pediatric centers;
4. Special field investigations of epidemics or individual cases;
5. Laboratory monitoring of infectious agents and therapeutic response in population samples;
6. Data on supply, use, and side effects of vaccines, toxoids, immunoglobulins;
7. Data on vector control activities such as insecticide use;
8. Immunity levels in samples of the population at risk;
9. Review of current literature on the disease;
10. Epidemiologic and clinical reports from other jurisdictions.

Epidemiologic monitoring based on individual and aggregated reports of infectious diseases provide data vital to planning interventions at the community level or for individual patients, along with other information sources such as hospital discharge data and monitoring of sentinel

centers. These may be specific medical or community sites that are representative of the population and are able to provide good levels of reporting to monitor an area or population group. A sentinel center can be a pediatric practice site, a hospital emergency room, or other location which will provide a "finger on the pulse" to assess suspicious changes occurring in the community. It can also include monitoring in a location previously known for disease transmission, such as Hong Kong in relation to influenza typing for vaccine planning, production, and distribution.

Epidemiologic analysis provided by government public health agencies should be published weekly, monthly, and annually and distributed to a wide audience of public health and health-related professionals throughout the country. Feedback is vital in order to promote involvement and improved quality of data, as well as to allow evaluation of local situations in comparison to other areas. In a federal system of government, national agencies report regularly on all state or provincial health patterns. State or provincial health authorities provide data to the counties and cities in their jurisdictions. Such data should also be readily available to researchers in other government agencies and academic settings for further research and analysis.

Notifiable diseases are those which a physician is legally required to report to state or local public health officials, by reason of their contagiousness, severity, frequency, or other public health importance (Table 4.2). Public health laboratory services provide validation of clinical and epidemiologic reports. They also provide day-to-day supervision of public health conditions, and can monitor communicable disease and vaccine efficacy and coverage. In addition, they support standards of clinical laboratories in biochemistry, microbiology, and genetic screening.

With newly emerging diseases and those spread far from their previously known habitat, and most especially because of the threats of pandemics such as SARS and more worryingly avian influenza, surveillance for human and animal disease is crucial to the societies we live in, including the global society. The first diagnosis of a

TABLE 4.2 Notifiable Infectious Diseases in the United States, 2007

AIDS/ HIV	Mumps
Arboviral disease	Pertussis (whooping cough)
Anthrax	Plague
Botulism	Poliomyelitis, paralytic or non-paralytic
Brucellosis (undulant fever)	Psittacosis
Chancroid	Q-fever
Chlamydia trachomatis, genital infection	Rabies (animal and human)
Cholera	Rocky Mountain spotted fever
Coccidiomycosis	Rubella and rubella congenital syndrome
Cryptosporidiosis	Rubella congenital syndrome
Cyclosporiasis	Salmonellosis
Diphtheria	Severe acute respiratory syndrome–associated coronavirus
Escherichia coli, Shiga toxin-producing (STEC)	Shigellosis
Erlichiosis	Smallpox
Giardiasis	Streptococcal disease, invasive group A
Gonorrhea	Streptococcal pneumonia, pediatric or drug-resistant invasive
Haemophilus influenzae, invasive disease	Streptococcal toxic shock syndrome
Hansen's disease (leprosy)	Syphilis (primary, secondary, latent, late, congenital)
Hantavirus pulmonary syndrome	Tetanus
Hemolytic uremic syndrome (post-diarrhea)	Toxic shock syndrome, streptococcal and non-streptococcal
Hepatitis, viral A, B, C, other	Trichinellosis
Influenza, pediatric mortality or novel influenza A	Tuberculosis
Legionnellosis	Tularemia
Lyme disease	Typhoid fever
Malaria	Vancomycin-resistant or intermediate *Staphylococcus aureus*
Measles	Varicella
Meningococcal disease	Vibriosis (non-cholera)
	Yellow fever

Note: Other diseases for which individual state monitoring may be required include: amebiasis, meningitis (aseptic and other bacterial), campylobacteriosis, dengue fever, genital herpes, genital warts, granuloma inguinale, leptospirosis, listeriosis, *Lymphogranuloma venereum*, mucopurulent cervicitis, nongonococcal urethritis, pelvic inflammatory disease, post-streptococcal disease, and others.
Source: Centers for Disease Control. 2007. www.cdc.gov/epo/mmwr/preview/mmwrhtml/0047449.htm [accessed October 14, 2007]

strange new disease entity may lead to its identification and practical measures to halt its spread. When it comes through anticipated or surprise epidemics and pandemics, and the real threat of bioterrorism, then multisectoral preparation and training are crucial.

HEALTH CARE–ASSOCIATED INFECTIONS

Health care institution–associated infections (HAI) are among the leading communicable and preventable causes of morbidity and mortality throughout the world. Nosocomial infections are those wherein a patient is exposed to and contracts disease while hospitalized. While great strides have been made in hospital sanitation, HAI still occurs in as many as 10 percent of admissions in developed countries. Recent CDC estimates place the number of nosocomial infections in the United States for 2002 at 1.7 million, a higher incidence than any notifiable disease. With a case mortality of nearly 6 percent, HAIs are also among the most deadly. Although progress has been made in HAI prevention, organisms implicated are becoming resistant to conventional therapy. In particular, methicillin-resistant *Staphylococcus aureus* (MRSA) which is among the most virulent and treatment-resistant bacteria, now accounts for over 50 percent of wound infections in many hospitals. Rare reports of vancomycin-resistant *S. aureus* (VRSA) cause alarm, proving antibiotic resistance transferred from other species. Treatment options for VRSA and vancomycin-resistant *Enterococcus* sp. are extremely limited, with concern these organisms could spread or become resistant to the few known effective therapies. The increasing number of immunodeficient patients has increased the importance of prevention of nosocomial infections (Box 4.4).

Where standards of infection control are lacking in both developed and developing countries, hospital staff and patients are vulnerable to serious infection. Of note, tuberculosis and hepatitis B exposure is common among health care workers, but preventable through airborne precautions and vaccination, respectively. In developing countries, deadly emerging viruses, such as avian influenza H5N1 and Ebola viruses infect nursing, medical, and other staff as secondary cases.

A great obstacle in quantifying the impact of HAI is lack of uniform and clear case definitions, as well as reliance, in most countries, on voluntary reporting by institutions. While many recommendations have been made, notably by the Society for Healthcare Epidemiology of America in 2003, no uniform regulations have been established to mandate reporting of HAIs. Much work has been focused on prevention, though. Standard Precautions (formerly known as Universal Precautions) are a set of basic practices by which health care workers may reduce the spread of nosocomial infection among patients, visitors, and staff, as well as protect health workers from occupationally acquired disease. These include adequate hand washing hygiene and use of protective barriers suited to specific risks. Expanded precautions and mandatory use of organism-specific clinical guidelines are necessary procedures in many health care institutions as protective measures. Organizational policy must be established for each institution by an integrated and authoritative department of infection control and epidemiology.

The cost of nosocomial infections is a major consideration in planning health budgets. Reducing the risk of HAI justifies substantial expenditures for hospital epidemiology and infection control activities. With diagnosis-related group (DRG) payment for hospital care (by diagnosis rather than by days of stay), the effective manager has a major incentive to minimize the risk of nosocomial infections to the improvement of patient care, because infections can greatly prolong hospital stays, raising patient dissatisfaction and health care costs.

Box 4.4 Health Care Facility Recommendations for Standard Precautions

Key Elements at a Glance

1. Hand hygiene
2. Gloves
3. Facial protection (eyes, nose, mouth)
4. Gown
5. Prevention of needlestick injuries
6. Respiratory hygiene and cough etiquette
7. Environmental cleaning
8. Linens
9. Waste disposal
10. Patient care equipment

Source: Adapted from WHO guidelines on hand hygiene in health care.

ENDEMIC AND EPIDEMIC DISEASE

An endemic disease is the continuous usual presence of a disease or infectious agent in a given geographic area or population group. Hyperendemic is a state of persistence of high levels of incidence of the disease. Holoendemic means that the disease appears early in life and affects most of the population, as in malaria or hepatitis A and B in some regions.

An epidemic is the occurrence in a community or region of a number of cases of an illness in excess of the usual or expected number of cases, or health-related behaviors (e.g., smoking) or events (e.g., motor vehicle accidents). The number of cases constituting an epidemic varies with the disease, and factors such as previous epidemiologic patterns of the disease, time and place of the occurrence, and the population involved must be taken

into account. A single case of a disease long absent from an area, such as polio, constitutes an epidemic, and therefore is a public health emergency because a clinical case may represent a hundred carriers with nonparalytic or subclinical poliomyelitis. Two to three or more cases such as measles or any unusual disease locally that are linked in time and place may be considered sufficient evidence of transmission and presumed to be an epidemic. A pandemic is occurrence of a disease on a wide scale over a very wide area, crossing international boundaries, affecting a large proportion of the world.

Epidemic Investigation

Each epidemic should be regarded as a unique natural experiment. The investigation of an epidemic requires preparation and field investigation in conjunction with local health and other relevant authorities. Verification of cases and the scope of the epidemic will require case definition and laboratory confirmation. Tabulation of known cases according to time, place, and person are important for immediate control measures and formulation of the hypothesis as to the nature of the epidemic. An epidemic curve is a graphic plotting of the distribution of cases by the time of onset or reporting, which gives a picture of the timing, spread, and extent of the disease from the time of the initial index cases and the secondary spread.

Epidemic investigation requires a series of steps. This starts with confirmation of the initial report and preliminary investigation, defining who is affected, determining the nature of the illness and confirming the clinical diagnosis, and recording when and where the first (index) and follow-up (secondary) cases occurred, and how the disease was transmitted. Samples are taken from index case patients (e.g., blood, feces, throat swabs) as well as from possible reservoirs (e.g., food, water, sewage, environment). A working hypothesis is established based on the first findings, taking into account all plausible explanations. The epidemic pattern is studied, establishing common source or risk factors, such as food, water, contact, environment, and drawing a time line of cases to define the epidemic curve.

How many are ill (the numerator) and what is the population at risk (the denominator) establish the attack rate; namely, the percentage of sick among those exposed to the common factor. What is a reasonable explanation of the occurrence: Is there a previous pattern, with the present episode a recurrence or new event? Consultation with colleagues and the literature helps to establish both a biological and epidemiologic plausibility. What steps are needed to prevent spread and recurrence of the disease? Coordination with relevant health and other officials and providers is required to establish surveillance and control systems, document and distribute reports, and respond to the public's right to know.

The first reports of excess cases may come from a medical clinic or hospital. The initial (sentinel or index) cases provide the first clues that may point to a common source. Investigation of an epidemic is designed to quickly elucidate the cause and points of potential intervention to stop its continuation. This requires skilled investigation and interpretation. The term "epidemiologic investigation" means a broad review of all evidence related to a topic, not just one epidemic or outbreak. Epidemiologic investigations have defined many public health problems. Rubella syndrome, Legionnaire's disease, AIDS, Lyme disease, and hantavirus diseases were first identified clinically when unusually large numbers of cases appeared with common features. The suspicions that were raised led to a search for causes and the identification of control methods.

A working hypothesis of the nature of an epidemic is developed based on the initial assessment, the type of presentation, the condition involved, and previous local, regional, national, and international experience. The hypothesis provides the basis for further investigation, control measures, and planning additional clinical and laboratory studies. Surveillance will then monitor the effectiveness of control measures. Communication of findings to local, regional, national, and international health reporting systems is important for sharing the knowledge with other potential support groups or other areas where similar epidemics may occur.

The Centers for Disease Control and Prevention (CDC), originally organized in 1946 as the Office for Malaria Control in War Areas, is part of the U.S. Public Health Service. As of 1993, the CDC had a budget of $1.5 billion, and its 7300 employees include epidemiologists, microbiologists, and many other professionals, By 2007, the CDC budget had reached $9 billion dollars with 8467 employees. The CDC includes national centers for environmental health and injury control, chronic disease prevention and health promotion, infectious diseases, prevention services, health statistics, occupational safety and health, and international health. Recently, however, budget reductions have imposed limits of capacity in such areas as overseas work.

The Epidemic Intelligence Service (EIS) of the CDC in the United States is an excellent model for the organization of the national control of communicable diseases. Clinicians are trained to carry out epidemiologic investigations as part of training to become public health professionals. EIS officers are assigned to state health departments, other public health units, and research centers as part of their training, carrying out epidemic investigation and special tasks in disease control.

The CDC, in cooperation with the WHO, has developed and offers free of charge a personal computer program to support field epidemiology, including epidemic investigations (EPI-INFO), which can be accessed and

downloaded from the Internet. This program should be adopted widely in order to improve field investigations, to encourage reporting in real time, and to develop high standards in this discipline.[1]

CDC's *Morbidity and Mortality Weekly Report* (*MMWR*) is a weekly publication of the CDC's epidemiologic data, also available free on the Internet. It includes special summaries of reportable infectious diseases as well as noncommunicable diseases of epidemiologic interest. *MMWR* publishes periodic special reports of important infectious and noninfectious diseases with comprehensive reviews of the literature and recent investigative work by the CDC and other organizations. *MMWR* published a review of Ten Great Achievements of Public Health in the United States in the Twentieth Century, which included control of communicable disease and vaccine-preventable diseases, as well as improvements in occupational health, maternal and child health, motor vehicle accidents, and cardiovascular and other chronic diseases and conditions (see Chapter 1).

CONTROL OF COMMUNICABLE DISEASES

Although an infectious disease is an event affecting an individual, it is transmissible to others, and therefore infection control requires both individual and community measures. Control of a disease is reduction in its incidence, prevalence, morbidity, and mortality. Elimination of a disease in a specified geographic area may be achieved as a result of intervention programs such as individual protection against tetanus; elimination of infections such as measles requires stoppage of circulation of the organism. Eradication is success in reduction to zero of naturally occurring incidence, such as with smallpox. Extinction means that a specific organism no longer exists in nature or in laboratories.

Public health applies a wide variety of tools for the prevention of infectious diseases and their transmission. It includes activities ranging from filtration and disinfection of community drinking water to environmental vector control, pasteurization of milk, and immunization programs (see Table 4.3). No less important are organized programs to promote self-protection, case finding, and effective treatment of infections to stop their spread to other susceptible persons (e.g., HIV, sexually transmitted infections, tuberculosis, malaria). Planning measures to control and eradicate specific communicable diseases is one of the principal activities of public health and remains so for the twenty-first century.

[1]Epidemiologic investigation may be arranged at the CDC or WHO by contacting the Epidemiology Program Office, Mailstop G34, Centers for Disease Control, Atlanta, Georgia 30333, or by telephone 404-639-2709 or fax 404-639-3296; or the World Health Organization, 1211 Geneva 27, Switzerland, or by telephone 41-22-791-2111 or fax 41-22-791-0746.

Treatment

Treating an infection once it has occurred is vital to the control of a communicable disease. Each person infected may become a vector and continue the chain of transmission. Successful treatment of the infected person reduces the potential for an uninfected contact person to acquire the infection. Bacteriostatic agents or drugs such as sulfonamides inhibit growth or stop replication of the organism, allowing normal body defenses to overcome the organism. Bactericidal drugs such as penicillin act to kill pathogenic organisms.

Traditional medical emphasis on single antibiotics has changed to use of multiple drug combinations for tuberculosis and more recently for hospital-acquired infections. Antibiotics have made enormous contributions to clinical medicine and public health. However, pathogenic organisms are able to adapt or mutate and develop resistance to antibiotics, resulting in drug resistance. Wide-scale use of antibiotics has led to increasing incidence of resistant organisms. Multidrug resistance constitutes one of the major public health challenges in the twenty-first century. Antiviral agents (e.g., Ribavirin) are important additions to medical treatment potential, as are "cocktails" of antiviral agents for management of HIV infection, known as highly active antiretroviral treatment (HAART). Prudent antibiotic use requires the attention of clinicians and their teachers as well as the public health community and health care managers, representing the interaction of health issues across the entire spectrum of services.

Methods of Prevention

Organized public health services are responsible for advocating legislation and for regulating and monitoring programs to prevent infectious disease occurrence and/or spread. They function to educate the population in measures to reduce or prevent the spread of disease.

Health promotion is one of the most essential instruments of infectious disease control. It promotes compliance and community support of preventive measures. These include personal hygiene and safe handling of water, milk, and food supplies. In sexually transmitted infections, health education is the major method of prevention.

Each of the infectious diseases or groups of infectious diseases has one or more preventive or control approaches (Table 4.3). These may involve the coordinated intervention of different disciplines and modalities, including epidemiologic monitoring, laboratory confirmation, environmental measures, immunization, and health education. This requires teamwork and organized collaboration.

Very great progress has been made in infectious disease control by clinical, public health, and societal means since 1900 in the industrialized countries and since the 1970s in the developing world. This is attributable to

TABLE 4.3 Methods of Prevention or Control of Infectious Diseases by Type of Organism

Control of major infectious diseases	Viruses	Bacteria	Parasites
Vaccination: pre-exposure to protect individuals and the community (herd immunity); post-exposure for individual protection (e.g., for rabies following animal bite, or contact after exposure to measles cases); or immunization of animals to prevent infected meat or milk transfer of disease to humans (e.g., brucellosis)	Rabies, polio, measles, rubella, mumps, hepatitis B, influenza, varicella, hepatitis A, human papillomavirus (HPV)	Diphtheria, pertussis, tetanus, tuberculosis, anthrax, brucella, pneumococcal pneumonia, *Haemophilus influenzae* type b	
Environmental measures: water and sewage control (e.g., chlorination of water to reduce burden of gastroenteric disease), vector control, antimosquito control measures (draining pooled water, larvicides, insecticides, repellants, protective bed nets and clothing)	Hepatitis A, rotaviruses, polio, arboviruses, tick- and mosquito-borne viruses	Salmonella, shigella, cholera, Legionnaire's disease, E. *coli*	Malaria, onchocerciasis, dracunculiasis, schistosomiasis, elephantiasis, worms
Education/social/behavior measures: to promote self-care and self-protection to reduce risk (e.g., safe sexual practices to prevent STIs and HIV), needle exchange, condom distribution among risk groups	HIV, human papillomavirus (HPV), hepatitis B and C	Diarrheal diseases, syphilis, gonorrhea, chancroid	Malaria, scabies, onchocerciasis, dracunculiasis
Animal and food control: to reduce transmission by pasteurization of milk, veterinary supervision of meat production and distribution, food hygiene and safety measures, radiation of food	Rabies	Brucellosis, coliforms, salmonellosis, shigellosis	Tapeworms
Case finding and treatment: to cure or prevent transmission and reduce the carrier population (e.g., blood, sputum screening)	Rabies, herpes, cytomegalovirus (CMV), HIV, hepatitis C	Tuberculosis, STIs, rheumatic fever	Malaria, worms, dracunculiasis, leprosy, onchocerciasis, schistosomiasis
Occupational measures: to protect persons exposed at place of work (e.g., immunization of food handlers, health care and child care workers)	HIV, hepatitis A and B, measles, rubella, arboviruses	Brucellosis, tuberculosis, anthrax	Hydatid cyst, trichinosis

a variety of factors, including organized public health services; the rapid development and wide use of new and improved vaccines and antibiotics; better access to health care; and improved sanitation, living conditions, and nutrition. Triumphs have been achieved in the eradication of smallpox and in the increasing control of other vaccine-preventable diseases. However, there remain serious problems with TB, STIs, malaria, new infections such as HIV, and an increase in multidrug-resistant organisms.

VACCINE-PREVENTABLE DISEASES

Vaccines are one of the most important tools of public health in the control of infectious diseases, particularly for child health. Vaccine-preventable diseases (VPDs) are those diseases preventable by currently available vaccines (Table 4.4). The term *vaccine* is derived from use of cowpox (vaccinia virus) to stimulate immunity to smallpox, first demonstrated by Jenner in 1796, and is generally used for all immunizing agents.

The body responds to invasion of disease-causing organisms by antigen–antibody reactions and cellular responses. Together, these act to restrain or destroy the disease-causing potential. Strengthening this defense mechanism through immunization has become one of the significant achievements of public health, preventing loss of literally millions of lives, and with very great potential for future generations as well (Box 4.5).

TABLE 4.4 Annual Incidence of Selected Vaccine-Preventable Infectious Diseases in Rates per 100,000 Population, Selected Years, United States, 1950–2004

Disease	1950	1960	1970	1980	1990	2000	2004
Diphtheria	3.8	0.5	0.2	0	0	0	0
Pertussis	79.8	8.2	2.1	0.8	1.8	2.9	8.9
Poliomyelitis	22.0	1.8	0	0	0	0	0
Measles	211.0	245.4	23.2	6.0	11.2	0.03	0.04
Mumps	na	na	55.6	3.9	2.2	0.08	0.09
Rubella	na	na	27.8	1.7	0.5	0.06	0
Hepatitis A	na	na	27.8	12.8	12.6	4.9	2.0
Hepatitis B	na	na	4.1	8.4	8.5	3.0	2.1

Note: na = not available.
Source: *Health United States*, 1998, 2006

Box 4.5 Definitions of Immunizing Agents and Processes

Vaccines: a suspension of live or killed microorganisms or antigenic portion of those agents presented to a potential host to induce immunity to prevent the specific disease caused by that organism. Preparation of vaccines may be from:

a. Live attenuated organisms which have been passed repeatedly in tissue culture or chick embryos so that they have lost their capacity to cause disease but retain an ability to induce antibody response, such as polio-Sabin, measles, rubella, mumps, yellow fever, BCG, typhoid, and plague.
b. Inactivated or killed organisms which have been killed by heat or chemicals but retain an ability to induce antibody response; they are generally safe but less efficacious than live vaccines and require multiple doses, such as polio-Salk, influenza, rabies, and Japanese encephalitis.
c. Cellular fractions, usually of a polysaccharide fraction of the cell wall of a disease-causing organism, such as pneumococcal pneumonia or meningococcal meningitis.
d. Recombinant vaccines produced by recombinant DNA methods in which specific DNA sequences are inserted by molecular engineering techniques, such as DNA sequences spliced to vaccinia virus grown in cell culture to produce influenza and hepatitis B vaccines.

Toxoids or antisera: modified toxins are made nontoxic to stimulate formation of an antitoxin, such as tetanus, diphtheria, botulism, and gas gangrene.

Immune globulin: an antibody-containing solution derived from immunized animals or human blood plasma, used primarily for short-term passive immunization (e.g., rabies, IgG globulin for immunocompromised persons).

Antitoxin: an antibody derived from serum of animals after stimulation with specific antigens and used to provide passive immunity (e.g., tetanus, snake and scorpion venom).

Source: Brooks, G. E., Butel, J. S., Morse, S. A. 2004. *Jawetz, Melnick and Adelberg's Medical Microbiology*, 23rd ed. Stamford, CT. Appleton & Lange; *Harrison's Textbook of Internal Medicine* (2005).

Immunization (vaccination) is a process used to increase host resistance to specific microorganisms to prevent them from causing disease. It induces primary and secondary responses in the human or animal body:

a. Primary response occurs on first exposure to an antigen. After a lag or latent period of 3–14 days (depending on the antigen), specific antibodies appear in the blood. Antibody production ceases after several weeks but memory cells that can recognize the antigen and respond to it remain ready to respond to a further challenge by the same antigen.
b. Secondary (booster) response is the response to a second and subsequent exposure to an antigen. The lag period is shorter than the primary response, with the peak being higher and lasting longer. The antibodies produced have a higher affinity for the antigen, and a much smaller dose of the antigen is required to initiate a response. Booster doses of vaccines are used to activate memory cells to strengthen immunity.
c. Immunologic memory exists even when circulating antibodies are insufficient to protect against the

antigen. When the body is exposed to the same antigen again, it responds by rapidly producing high levels of antibody to destroy the antigen before it can replicate and cause disease.

Immunization protects susceptible individuals from communicable disease by administration of a living modified agent, a subunit of the agent, a suspension of killed organisms, or an inactivated toxin (see Table 4.5) to stimulate development of antibodies to that agent. In disease control, individual immunity may also protect another individual.

Herd immunity occurs when sufficient numbers of persons are protected (naturally or by immunization) against a specific infectious disease, reducing circulation of the organism, and thereby lowering the chance of an unprotected person becoming infected. Each pathogen has different characteristics of infectivity, and therefore different levels of herd immunity are required to protect the nonimmune individual.

Immunization Coverage

The critical proportion of a population that must be immunized in order to interrupt local circulation of the organism varies from disease to disease. Eradication of smallpox was achieved with approximately 80 percent world coverage, followed by concentration on new case findings and immunization of contacts and surrounding communities.

TABLE 4.5 Development of Vaccines by Period of Development and Type of Vaccine

Period/Century	Live attenuated	Killed, whole organism	Purified protein or polysaccharide	Genetically engineered
Eighteenth century	Smallpox (1798)	na	na	na
Nineteenth century	Rabies (1885)	Hog cholera (1886)	Diphtheria antitoxin (1888)	na
	Cholera (1896)	Typhoid (1896)		
	Plague (1897)			
Early twentieth century	BCG tuberculosis (1927)	Pertussis (1926)	Diphtheria (1923)	na
	Yellow fever (1935)	Influenza (1936)	Tetanus toxoid (1927)	
		Rickettsia (1936)	Influenza A (1936)	
Post–World War II	Yellow fever (1953)	Influenza (1945)	Diphtheria toxoid (1949)	na
	Polio, Sabin (1963)	Tetanus toxoid (1949)	*Pneumococcus* (1976, 1983)	
	Measles (1963)	Typhoid (1952)	*Meningococcus* (1962)	
	Mumps (1967)	Polio, Salk (1955)	Tick-borne encephalitis	
	Rubella (1970)	Anthrax (1970)		
	MMR (1971)			
1980–1999	Adenovirus (1980)	Rabies (1980, human diploid cell)	*Haemophilus influenzae* type b (1985)	Hepatitis B (1987) recombinant (yeast or mammalian cell derived)
	Typhoid (1992, 1995) (*Salmonella* Type21a, Vi)	Japanese encephalitis (1993)	Hepatitis B (1981, plasma)	
	Varicella (1995)		Pertussis, acellular (1993)	
	Lyme disease (1998)	Hepatitis A (1995)		
	Rotavirus (1998)			
2000–2010	New vaccines for pneumococcal, meningococcal disease, influenza, parainfluenza, Human papillomavirus (HPV), respiratory syncytial virus			
Anticipated	*H. pylori*, *Streptococcus*, HIV, hepatitis C, adenoviruses, malaria			

Note: Years developed or licensed in the United States.
na: Not available.
Centers for Disease Control. Vaccines universally recommended for children — United States, 1990–98. *Morbidity and Mortality Weekly Report*, 48.243–248.
Sources: Modified from Plotkin, S. A., Orentein, W. A. 2003. *Vaccines*, 4th ed. Philadelphia: W. B. Saunders.

For highly infectious diseases such as measles, immunization coverage of over 95 percent is needed to achieve local eradication.

Immunization coverage in a community must be monitored in order to gauge the extent of protection and need for program modification to achieve targets of disease control. Immunization coverage is expressed as a proportion in which the numerator is the number of persons in the target group immunized at a specific age, and the denominator is the number of persons in the target cohort who should have been immunized according to the accepted standard:

$$\text{Vaccine coverage} = \frac{\text{no. persons immunized in specific age group}}{\text{no. persons in the age group during that year}} \times 100$$

Immunization coverage in the United States is regularly monitored by the National Immunization Survey, a telephone-based questionnaire of households from all 50 states, as well as selected areas at high risk for inadequate levels of vaccination. An initial telephone survey is followed by confirmation, where possible, from documentation from the parents or health care providers. The childhood immunization survey for 2006 examined children aged 19–35 months. The results show 85 percent of U.S. children having received four or more (4+) doses of DTaP (diphtheria, tetanus, acellular pertussis), 93 percent with three or more (3+) doses of oral or injected polio vaccine, and 93 percent with three or more (3+) doses of *Haemophilus influenzae* type b (Hib). Hepatitis B coverage (3+) greatly increased to 93 percent, while institution of pneumococcal (3+) and varicella (1+) vaccination policies has rapidly achieved 87 percent and 89 percent, respectively. Despite these gains, only 77 percent of children received all vaccinations at recommended ages.

Present technology allows for control or eradication of important infectious diseases that still cause millions of deaths globally each year. Other important infectious diseases are still not subject to vaccine control because of difficulties in their development. In some cases, a microorganism can mutate with changes. Viruses can undergo antigenic shifts in their molecular structure, producing completely new subtypes of the organism. Hosts previously exposed to other strains may have little or no immunity to the new strains.

Antigenic drift refers to relatively minor antigenic changes which occur in viruses. This is responsible for frequent epidemics. Antigenic shift is believed to explain the occurrence of new strains of influenza virus, necessitating annual reformulation of the influenza vaccine. New variants of poliovirus strains are similar enough to three main types that immunity to one strain is carried over to the new strain. Molecular epidemiology is a powerful genetic technique used to determine geographic origin, permitting tracking of the spread of infectious organisms and epidemics.

Combination of more than one vaccine is now common practice with a trend to enlarging the cocktail of vaccines in order to minimize the number of injections and visits required. This reduces staff time and costs, as well as increasing convenience and compliance by the public. There are virtually no contraindications to use of multiple antigens simultaneously. Examples of vaccine cocktails include DTaP in combination with *Haemophilus influenzae* type b, poliomyelitis, varicella, or MMR (measles, mumps, and rubella) vaccines.

Interventions in the form of effective vaccination save millions of lives each year and contribute to improved health of countless children and adults throughout the world. Vaccination is accepted as one of the most cost-effective health interventions currently available. Continuous policy review is needed regarding allocation of adequate resources, logistical organization, and continued scientific effort to seek effective, safe, and inexpensive vaccines for other important diseases such as malaria and HIV. Molecular technology, producing recombinant vaccines such as those for hepatitis A and B, holds promise for important vaccine breakthroughs in the decades ahead.

Internationally, much progress was made in the 1980s in the control of VPDs. At the end of the 1970s, fewer than 10 percent of the world's children were being immunized. WHO, UNICEF, and other international organizations mobilized to promote an Expanded Programme on Immunization (EPI) with a target of reaching 80 percent coverage by 1990. WHO in 2007 reports that diphtheria, pertussis and tetanus (DPT 3 doses), polio (3 doses), and measles coverages globally reached 80–90 percent in 2006. *Haemophilus influenzae* b vaccination (3 doses) reached 90 percent of the population of the Americas region, 44 percent of the European region, and 24 percent of African region of WHO in 2006. Immunization is preventing some 3 million child deaths annually in developing countries. Bacille Calmette-Guérin (BCG) coverage internationally rose from 31 percent to 89 percent; poliomyelitis with OPV (three doses) from 24 percent to 85 percent, and tetanus toxoid for pregnant women from 14 percent to 57 percent. Recent declines in coverage have occurred in many parts of the world though, notably in Sudan, Burma, and other regions affected by violent conflicts.

The challenge remains to achieve control or eradication of VPDs, thus saving millions more lives. Part of the HFA stresses the EPI approach, which includes immunization against diphtheria, pertussis, tetanus, poliomyelitis, measles, and tuberculosis. An extended form of this is the EPI PLUS program which combines EPI with immunization against hepatitis B and yellow fever and, where appropriate, supplementation with vitamin A and iodine. The success in international eradication of smallpox has been

followed with major progress toward eradication of poliomyelitis, measles, and other important infectious diseases.

Diphtheria

Diphtheria is an acute bacterial disease of the tonsils, nasopharynx, and larynx caused by the organism *Corynebacterium diphtheriae*. It occurs in colder months in temperate climates where the organism is present in human hosts and is spread by contact with patients or carriers. It has an incubation period of 2–5 days. In the past, this was primarily an infection of children and was a major contributor to child mortality in the pre-vaccine and pre-antibiotic eras. Diphtheria has been virtually eliminated in countries with well-established immunization programs.

In the 1980s, an outbreak of diphtheria occurred in the countries of the former Soviet Union among people over age 15. It reached epidemic proportions in the 1990s, with 140,000 cases (1991–1995) with 1100 deaths in 1994 in Russia alone. This indicates a failure of the vaccination program in several respects: it used only three doses of DPT in infancy, no boosters were given at school age or subsequently, the efficacy of diphtheria vaccine may have been low, and coverage was below 80 percent.

Efforts to control the present epidemic include mass vaccination campaigns for persons over 3 years of age with a single dose of DT (diphtheria and tetanus) and increasing coverage of routine DPT vaccines to four doses by age 2 years. The epidemic and its control measures have led to improved coverage with DT for those over 18 years, and 93 percent coverage among children aged 12–23 months.

WHO recommends three doses of DPT in the first year of life and a booster at primary school entry, as well as at enrollment at college, military, or other organized settings. This is considered by many to be insufficient to produce long-lasting immunity. The United States and other industrialized countries use a four-dose schedule and recommend periodic boosters for adults with DT.

Pertussis

Pertussis is an acute bacterial disease of the respiratory tract caused by the bacillus *Bordetella pertussis*. After an initial coldlike (catarrhal) stage, the patient develops a severe cough which comes in spasms (paroxysms). The disease can last 1–2 months. The paroxysms can become violent and may be followed by a characteristic crowing or high-pitched inspiratory whooping sound, followed by expulsion of tenacious clear sputum, often followed by vomiting. In poorly immunized populations and those with malnutrition, pneumonia often follows, and death is common.

Pertussis declined dramatically in the industrialized countries as a result of widespread coverage with DPT. However, because the pertussis component of early vaccines caused rare reactions, many physicians and parents avoided its use, instead opting for DT alone, leaving children susceptible to infection. During the 1970s in the United Kingdom, many physicians recommended against vaccination with DPT. As a result, pertussis incidence increased with substantial mortality rates. This led to a reappraisal of the immunization program, with institution of incentive payments to general practitioners for completion of vaccination schedules. As a result of these measures, vaccination coverage, with resulting pertussis control, improved dramatically in the United Kingdom. A new acellular vaccine is now in widespread use and will be safer with fewer and less severe reactions in infants, increasing the potential for improved confidence and support for routine vaccination. The new vaccine is used in the United States and other industrialized countries, and forms part of the U.S. recommended vaccination schedule. Although most western European countries are advanced in use of vaccines, there is no Europe-wide equivalent of the CDC-recommended immunization schedule for the region, which will be coming up for discussion in European Union health forums.

The CDC reports estimates of childhood vaccination coverage in the United States with $\geq$3 doses of pertussis-containing vaccine have exceeded 90 percent since 1994. However, reported pertussis cases increased from a historic low of 1010 cases in 1976 to 11,647 in 2003, with a substantial increase in reported cases among adolescents, who become susceptible to pertussis approximately 6–10 years after their childhood vaccination. This is attributed to waning immunity and lack of booster doses, so booster doses in adolescence are now recommended.

Pertussis continues to be a public health threat and recurs wherever there is inadequate immunization in infancy. In addition, recent epidemics have been noted in adults who have lost childhood immunity. While the disease generally follows a milder course in healthy adults, this raised concerns of a reservoir for infection of children and the immunocompromised. To eliminate this risk, pertussis booster vaccination is recommended during adolescence and again in adulthood.

Tetanus

Tetanus is an acute disease caused by an exotoxin of the tetanus bacillus (*Clostridium tetani*) which grows anaerobically at the site of an injury. The bacillus is universally present in the environment and enters the human body via penetrating injuries. Following an incubation period of 3–21 days, it causes an acute condition of painful muscular contractions. Unless there is modern medical care available, patients are at risk of high case fatality rates of 30–90 percent (highest in infants and the elderly).

Antitetanus serum (ATS) was discovered in 1890, and during World War I, ATS contributed to saving the lives

of many thousands of wounded soldiers. Tetanus toxoid was developed in 1993. The organism, because of its universal presence in the environment, cannot be eradicated. However, the disease can be controlled by effective immunization of every child during infancy and school age. Adults should receive routine boosters of tetanus toxoid once very decade.

Newborns are infected by tetanus spores (tetanus neonatorum) where unsanitary conditions or practices are present. It can occur when traditional birth attendants at home deliveries use unclean instruments to sever the umbilical cord, or dress the severed cord with contaminated material. Tetanus neonatorum remains a serious public health problem in developing countries. Immunization of pregnant women and women of childbearing age is reducing the problem by conferring passive immunity to the newborn. The training of traditional birth attendants in hygienic practices and the use of medically supervised birth centers for delivery also decrease the incidence of tetanus neonatorum.

Elimination of tetanus neonatorum was made a health target by the World Summit of Children in 1990. In that year, the number of deaths from neonatal tetanus was reported by WHO as 25,293 infants worldwide, declining to 8376 in 2006 (112 countries reporting). Immunization of pregnant women increased from under 20 percent in 1984 to 69 percent in 2006.

Tetanus cases have declined dramatically in the United States, but the disease still occurs mainly among older adults. The CDC reports during 1990–2001, a total of 534 cases of tetanus were reported; 301 (56 percent) cases occurred among adults aged 19–64 years and 201 (38 percent) among adults aged $\geq$65 years. Data from a national population-based serosurvey indicated the prevalence of immunity to tetanus was >80 percent among adults aged 20–39 years but declined with increasing age. This supports current recommendations to give booster doses of tetanus (with diphtheria) vaccine for adolescents and adults every 10 years.

Poliomyelitis

Poliovirus infection may be asymptomatic or cause an acute nonspecific febrile illness. It may reach more severe forms of aseptic meningitis and acute flaccid paralysis with long-term residual paralysis or death during the acute phase. Poliomyelitis is transmitted mainly by direct person-to-person contact, but also via sewage contamination. Large-scale epidemics of disease, with attendant paralysis and death, occurred in industrialized countries in the 1940s and 1950s, engendering widespread fear and panic and thousands of clinical cases of "infantile paralysis."

Growth of the poliovirus by John Enders and colleagues in tissue culture in 1949 led to development and wide-scale testing of the first inactivated (killed) polio vaccine by Jonas Salk in the mid-1950s and great hope and outstanding success in the control of this much feared disease. Development of the live attenuated oral poliomyelitis vaccine (OPV) by Albert Sabin, licensed in 1960, added a major new dimension to poliomyelitis control because of the effectiveness, low cost, and ease of administration of the vaccine. The two vaccines in their more modern forms, enhanced strength inactivated polio vaccine (eIPV), and triple oral polio vaccine (TOPV), have been used in different settings with great success.

Oral polio vaccine (OPV) induces both humoral and cellular, including intestinal, immunity. The presence of OPV in the environment by contact with immunized infants and via excreta of immunized persons in the sewage gives a booster effect in the community. Immunization using OPV, in both routine and National Immunization Days (NIDs) has proven effective in dramatically reducing poliomyelitis and circulation of the wild virus in many parts of the world. Use of the eIPV produces early and high levels of circulating antibodies, as well as protecting against the vaccine-associated disease.

In rare cases, OPV can cause vaccine-associated paralytic poliomyelitis (VAPP), with a risk of 1 case per 520,000 with initial doses, and 1 case per over 12 million with subsequent doses. Approximately 8 to 10 cases of VAPP occurred annually in the United States during the 1990s following the elimination of natural transmission. The CDC changed recommendations to IPV use in 1999, out of concern that VAPP risk would outweigh risk of local wild polio from imported cases. Many developed countries have followed suit. While this eliminates risk for VAPP, concerns have risen that herd immunity may be reduced due to shorter memory and lower intestinal immunity noted with IPV use.

Controversy as to the relative advantages of each vaccine continues. The OPV program of mass repeated vaccination in control of poliomyelitis in the Americas established the primacy of OPV in practical public health, and the momentum to eradicate poliomyelitis is building. OPV requires multiple doses to achieve protective antibody levels. Where there are many enteroviruses in the environment, interference in the uptake of OPV may result in cases of paralytic poliomyelitis among persons who have received 3 or even 4 doses of adequate OPV. Use of IPV as initial protection eliminates this problem. During the 1970s and 1980s, a combined approach bolstering IPV immunity with OPV boosters showed promise in Gaza and Israel, where natural poliovirus was eradicated. Although sequential use of IPV and OPV was adopted as part of the routine infant immunization program in the United States in 1997, current programs use IPV alone. IPV has been adopted as the exclusive polio vaccine in most of the industrialized countries, while developing countries continue relying on the less costly and easier to administer OPV. Mop-up campaigns using monovalent

OPV (Type 1) in still-endemic areas such as specific regions of India and Nigeria are being promoted.

There are concerns that exclusive use of either vaccine alone will not lead to the desired goal of eradication of poliomyelitis. In 1988, the polio eradication initiative was launched. Progress in global eradication of polio has been impressive. Global coverage of infants with three doses of OPV reached 85 percent in 2005 as compared to 83 percent in 1995 (UNICEF). During the same period, OPV coverage in the the African region of WHO increased from 51 percent in 2000 to 75–80 percent in 2006. National immunization days (NIDs) are conducted in many countries throughout the world, achieving coverage of over 400 million children annually. Mop-up operations to reinforce coverage of children in still-endemic areas are proceeding, along with increased emphasis on acute flaccid paralysis (AFP) monitoring. Worldwide clinical cases from wild poliovirus have been reduced to 2000 per year in 2006. By the end of 2006 four countries remained endemic for polio: India (676 cases); Pakistan (40 cases); Afghanistan (31 cases); and Nigeria (1125 cases); another 13 countries in Africa, the Middle East, and Southeast Asia reported clinical cases of poliomyelitis due to active transmission in 2006.

With continued national and international emphasis, and support of WHO, Rotary International, UNICEF, donor countries, there is real prospect of a world without polio.

Measles

Measles is an acute disease caused by a virus of the *Paramyxovirus* family. It is highly infectious with a very high ratio of clinical to subclinical cases (99/1). Measles has a characteristic clinical presentation with fever, rhinorrhea, white spots (Koplik spots) on the membranes of the mouth, and a red blotchy rash appearing on day 3–7 lasting 4–7 days. Mortality rates are high in young children with compromised nutritional status, especially vitamin A deficiency.

The measles virus evolved from a virus disease of cattle (rinderpest) some 3000–5000 years ago, becoming an important disease of humans with high mortality rates in debilitated, poorly nourished children, and significant mortality and morbidity even in industrialized countries. In the pre-vaccine era, measles was endemic worldwide, and remains a major childhood infectious disease.

Single-dose immunization failed to meet control or eradication requirements even in the most developed parts of the world. A live vaccine, licensed in 1963, was later replaced by a more effective and heat-stable vaccine, but still with a primary vaccination failure rate (i.e., fails to produce protective antibodies) of 4–8 percent, and secondary failure rate (i.e., produces antibodies but protection is lost over time) of 4 percent. A two-dose policy incorporates a booster dose, usually at school age, in addition to maximum feasible infant coverage of children in the 9–15 month period (timing varies in different countries). Catch-up campaigns among school-age children should be carried out until the routine two-dose policy has time to take full effect. Nearly universal primary education in developing countries offers an opportunity for mass coverage of school-age children with a second dose of measles vaccine and a resulting increase of herd immunity to reduce the transmission of the virus. The two-dose policy adopted in many countries should be supplemented with catch-up campaigns in schools to provide the booster effect for those previously immunized and to cover those previously unimmunized, especially in developing countries.

The CDC considers that domestic transmission in the United States has been interrupted and that most localized outbreaks were traceable to imported cases. South America and the Caribbean countries are now considered free from indigenous measles, based on their successful use of NIDs, although a large epidemic occurred in 1999 in Brazil. Eradication of measles is feasible in the second decade of this century, if a two-dose policy is used and sustained with high priority globally, supplemented by catch-up campaigns to older children and young adults, and outbreak control.

Measles eradication is one of the central targets on WHO's agenda, with emphasis placed on reducing mortality and secondary on gradual eradication of the disease. Measles deaths have fallen by 60 percent worldwide since 1999 from an estimated 873,000 deaths in 1999 to 345,000 in 2005. In Africa in this period, measles deaths fell by 75 percent, from an estimated 506,000 to 126,000, with 90 percent of children under the age of five mostly dying from complications such as severe diarrhea, pneumonia, and encephalitis.

International transmission of the virus in carriers has led to importation and subsequent epidemics even in countries thought to have achieved local eradication, with outbreaks in 2006–2008 in the United Kingdom, Switzerland (2250 cases), Austria, France, Italy, and other countries. Israel had an epidemic of over 1200 cases in 2007–2008 following an imported case. The Health Protection Agency in the United Kingdom in July 2008 declared measles to be endemic for the first time in 14 years due to a decade of poor coverage with the measles vaccine. The United States had an annual average of 64 cases during 2000–2007, but an increase in 2008.

The WHO strategy of partnership with national governments and NGOs such as he Measles Initiative, GAVI, and others, includes:

- provision of one dose of measles vaccine for all infants via routine health services;
- a second dose for children through mass vaccination campaigns;
- effective surveillance for measles; and
- enhanced care, including the provision of supplemental vitamin A.

WHO has promoted measles vaccination campaigns along with other life-saving interventions such as bed nets

to protect against malaria, deworming medicine, and vitamin A supplements to expand the contact occasion to reduce child death rates in keeping with the Millennium Development Goals between 1990 and 2015. Elimination of measles as a public health problem, and even eradication, are feasible goals in the second decade of the next century and critical to achieving the Millennium Development Goals target of reducing child mortality by the year 2015. This topic deserves to be one of the highest professional and political priorities of international and national donor and public health agencies as well as national governments.

Mumps

Mumps is an acute viral disease characterized by fever, swelling, and tenderness usually of the parotid glands, but also other glands. The incubation period ranges between 12 and 25 days. Orchitis, or inflammation of the testicles, occurs in 20–30 percent of postpubertal males and oophoritis, or inflammation of the ovaries, in 5 percent of postpubertal females. Sterility is an extremely rare result of mumps. Central nervous system involvement can occur in the form of aseptic meningitis, almost always without sequelae. Encephalitis is reported in 1–2 per 10,000 cases with an overall case fatality rate of 0.01 percent. Pancreatitis, neuritis, nerve deafness, mastitis, nephritis, thyroiditis, and pericarditis, although rare, may occur. Most persons born before 1957 are immune to the disease, because of the nearly universal exposure to the disease before that time.

The live attenuated vaccine introduced in the United States in 1967 is available as a single vaccine or in combination with measles and rubella as the measles-mumps-rubella (MMR) vaccine. It provides long-lasting immunity in 95 percent of cases. Mumps vaccine is now recommended in a two-dose policy with the first dose of MMR given between 12 and 15 months of age and a second dose given either at school entry or in early adolescence. MMR in two doses is now standard policy in the United States, Sweden, Canada, Israel, and other countries. The incidence of mumps has consequently declined rapidly. However, it is still a threat.

During 2004–2005, the United Kingdom experienced a nationwide epidemic of mumps, which peaked during 2005 when over 56,000 cases were reported in England and Wales, mostly aged 15–24 years, and most of whom had not been eligible for routine mumps vaccination. Figure 4.2 shows the epidemic curve during the period 2004–2005, as published in *MMWR*. The episode can be traced back to the period of controversy regarding use of MMR vaccine and increased susceptibility in a partly immunized population in the age group that received only one dose of the vaccine, if at all.

Poland also experienced a major outbreak of mumps in 2005–2006, mostly among children aged 5–9 years. The United Kingdom had more than 100,000 mumps cases in 2004 to 2005; the United States had 4000 cases in a Midwest outbreak in 2006. Canada reported more than 450 cases of mumps among university students in the spring of 2007 (WHO; U.S. Centers for Disease Control; Health Canada). In the tourist summer periods of 2004 and 2005, 39 patients with mumps had been hospitalized in Crete and Greece, and almost all were young tourists from Britain. The disease is spreading among the Greek population as well; 6 cases have been reported. Many countries in Europe still do not use MMR or a two-dose policy; thus they are vulnerable to mumps along with rubella outbreaks. MMR vaccination should be adopted as an international standard with two doses for all children and catch-up for school-age children. Local eradication of this disease is worthwhile and should be part of a basic international immunization program.

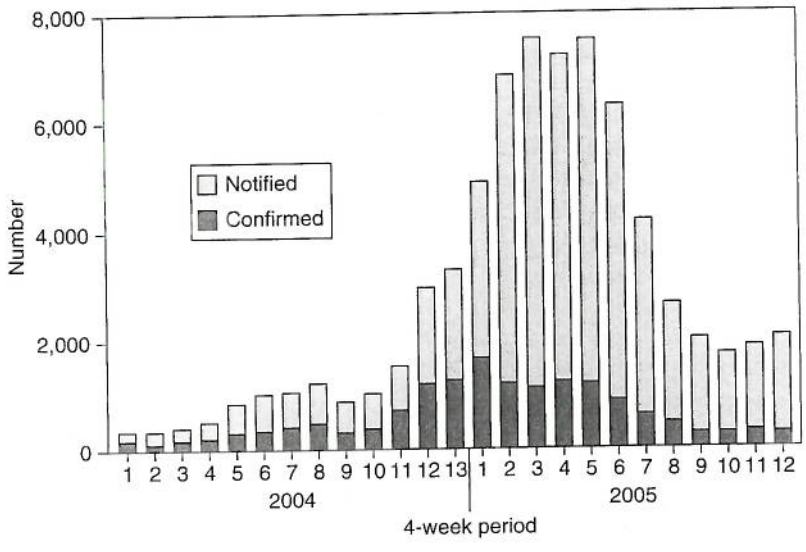


FIGURE 4.2 Curve of mumps epidemic, United Kingdom, 2004–2005. Source: Centers for Disease Control. 2006. Mumps Epidemic — United Kingdom, 2004–2005. *Morbidity and Mortality Weekly Report*, 55:173–175.

Rubella

Rubella (German measles) is generally a mild viral disease with lymphadenopathy and a diffuse, raised red rash. Low-grade fever, malaise, coryza, and lymphadenopathy characterize the prodromal period. The incubation period is usually 16–18 days. Differentiation from scarlet fever, measles, or other febrile diseases with rash may require laboratory testing and recovery of the virus from nasopharyngeal, blood, stool, and urine specimens (Box 4.6).

Congenital rubella syndrome (CRS) occurs with single or multiple congenital anomalies including deafness, cataracts, microophthalmia, congenital glaucoma, microcephaly, meningoencephalitis, congenital heart defects, and others. Moderate and severe cases are recognizable at birth, but mild cases may not be detected for months or years after birth. Insulin-dependent diabetes is suspected as a late sequela of congenital rubella. Each case of CRS is estimated to cost some $250,000 in health care during the patient's lifetime.

Prior to availability of the attenuated live rubella vaccine in 1969, the disease was universally endemic, with epidemics or peak incidence every 6–9 years. In unvaccinated populations, rubella is primarily a disease of childhood. In areas where children are well-vaccinated, adolescent and young adult infection is more apparent, with epidemics in institutions, colleges, and among military personnel.

A sharp reduction of rubella cases was seen in the United States following introduction of the vaccine in 1970, but increased in 1978, following rubella epidemics in 1976–1978. A further reduction in cases was followed by a sharp upswing of rubella and CRS in 1988–1990. An outbreak of rubella among the Amish in the United States, who refuse immunization on religious grounds, resulted in seven cases of CRS in 1991. It is now thought that vaccination of sufficient numbers in the United States reduced circulation of the virus and protected most vulnerable groups in the population. Most industrialized countries adopted MMR in the 1990s and a two-dose policy subsequently. Rubella and CRS incidence dropped dramatically. Controversy in the United Kingdom in the early 2000s led to reduced MMR usage and an increase in cases of measles and rubella. This was subsequently improved by providing incentive payments for general practitioners with 100 percent age-specific immunization coverage.

Some parts of Europe failed to adopt MMR vaccine use and have suffered recurrent outbreaks of these diseases. A number of outbreaks were reported in 2005–2007. Poland reported 7946 cases of rubella in 2005 (20.8 per 100,000 population), an increase of 64 percent compared to 2004. MMR was added to the routine immunization schedule at the end of 2003.

In November 2003, Italy approved a national plan for the elimination of measles and congenital rubella, with the aim of reducing and maintaining the incidence of congenital rubella syndrome (CRS) to less than 1 case per 100,000 live births by 2007.

As of 2007, there is no common recommended childhood immunization program for the European Union or for European Region of WHO. This leaves each country to develop its own and provides no guidelines for countries in transition from the socialist period operating with obsolescent immunization practices and only very slowly adopting western standards. Many have not yet adopted MMR. WHO considers eradication of measles and rubella of higher priority than mumps, but suggests the combination MMR vaccine be used.

In the past, immunization policy for rubella in some countries was to vaccinate schoolgirls aged 12 and women after pregnancy to protect them for the period of fertility. The current approach is to give a routine dose of MMR in early childhood, followed by a second dose in early school age to reduce the pool of susceptible persons. Women of reproductive age should be tested to confirm immunity before pregnancy and immunized if not already immune. Should a woman become infected during pregnancy, termination of pregnancy as previously recommended is now managed with hyperimmune globulin.

The infection of pregnant women during their first trimester of pregnancy is the primary public health implication of rubella. The emotional and financial burden of CRS, including the cost of treatment of its congenital defects, makes this vaccination program cost-effective. Its inclusion in a modern immunization program is fully justified. Elimination of CRS syndrome should be one of the primary goals of a program for prevention of VPDs in developed and developing countries. Adoption of MMR and the two-dose policy will gradually lead to eradication of rubella and rubella syndrome.

Box 4.6 Discovery of Rubella Syndrome

In 1942, Norman Gregg, an Australian ophthalmologist, noted an epidemic of cases of congenital cataract in newborns associated with a history of rubella in the mother during the first trimester. Subsequent investigation demonstrated that intrauterine death, spontaneous abortion, and congenital anomalies occur commonly when rubella occurs early in pregnancy.

Viral Hepatitis

Viral hepatitis is a group of diseases of increasing public health importance due to its large-scale worldwide prevalence, its serious consequences, and our increasing ability to take preventive action. Viral hepatic infectious diseases each have specific etiologic, clinical, epidemiologic,

serologic, and pathologic characteristics. They have important short- and long-term sequelae. Vaccine development is of high priority for control and ultimate eradication.

Hepatitis A

Hepatitis A (HAV) is mainly transmitted by the fecal–oral route. Clinical severity varies from a mild illness of 1–2 weeks to a debilitating illness lasting several months. The norm is complete recovery within 9 weeks, but a fulminating or even fatal hepatitis can occur. Severity of the disease worsens with increasing age. HAV is sporadic/endemic worldwide.

Improving sanitation raises the age of exposure, with accompanying complications. It now occurs particularly in persons from industrialized countries who are exposed to situations of poor hygiene, contaminated food products, or among young adults when traveling to areas where the disease is endemic. Common source outbreaks occur in school-age children and young adults from case contact or from food contaminated by infected handlers. Hepatitis A may be a serious public health problem in a disaster situation.

Prevention involves improving personal and community hygiene, with safe chlorinated water and proper food handling. Short-term risk for infection for people exposed to HAV may be reduced with prompt administration of HAV immune globulin. Hepatitis A vaccine is now recommended for all children over 12 months of age, as well as for persons traveling to endemic areas or at increased risk of exposure or morbidity. CDC reports 33 percent of the U.S. population were ever infected with HAV, but there is no chronic carrier state. HAV immunization is being adopted for routine prevention programs in some countries, including the United States, and is used for pre-exposure prevention, but immune globulin is still used for post-exposure protection. As costs of the vaccine come down, its widespread routine use may be recommended.

Hepatitis B

Hepatitis B (HBV) was once thought to be transmitted only by injections of blood or blood products. It is now known to be present in all body fluids and easily transmissible by household and sexual contact, perinatal spread from mother to newborn, and between toddlers. However, it is not usually spread by the oral–fecal route.

Hepatitis B virus is endemic worldwide and is especially prevalent in developing countries. Carrier status with persistent viremia is estimated by CDC to be 1.25 million in the United States, with 4.9 percent of the population ever infected. Carrier rates are 5–8 percent in sub-Saharan Africa but between 8 and 15 percent of babies become infected in some parts of the world, so that routine immunization is recommended. Carriers have detectable levels of HBsAg, the surface antigen (i.e., Australian antigen), in their blood.

Transmission from mother to child and between children by unsafe injections and sexual contact are common. High-risk groups who should be immunized in developed countries include health care workers, intravenous drug users; men who have sex with men; persons with high numbers of sexual partners; those receiving tattoos, body piercing, or acupuncture treatments; and residents or staff of institutions such as group homes and prisons. Immunocompromised and hemodialysis patients are commonly carriers of HBV. HBV may also be spread in a health system by use of inadequately sterilized reusable syringes, as in China and the former Soviet Union. Transmission is reduced by screening blood and blood products for HBsAg and strict technique for handling blood and body fluids in health settings.

HBV is clinically recognizable in less than 10 percent of infected children but is apparent in 30–50 percent of infected adults. Clinically HBV has an insidious onset with anorexia, abdominal discomfort, nausea, vomiting, and jaundice. The disease can vary in severity from subclinical, very mild, to fulminating liver necrosis and death. It is a major cause of primary liver cancer, chronic liver disease, and liver failure, all devastating to health and expensive to treat.

Hepatitis B virus is considered to be the cause of 60 percent of primary cancer of the liver in the world and the most common carcinogen after cigarette smoking. The WHO estimates that more than 2 billion people alive today have been infected with HBV. It is also estimated that 350 million persons are chronic carriers of HBV, with an estimated 1–1.5 million deaths per year from cirrhosis or primary liver cancer. This makes hepatitis B control a vital issue in the revision of health priorities in many countries.

Strict discipline in blood banks and testing of all blood donations for HBV, as well as HIV, and hepatitis C, is mandatory, with destruction of those donations with positive tests. Contacts should be immunized following exposure with HBV immunoglobulin and HBV vaccine. The inexpensive recombinant HBV vaccine should be adopted by all countries and included in routine vaccination of infants. Catch-up immunization for older children is also desirable. Immunization programs should include those exposed at work, such as health, prison, and sex workers and adults in group settings. HBV immunization has been included in WHO's EPI-PLUS expanded program of immunization.

Hepatitis C

First identified in 1989, and previously known as non-A, non-B hepatitis, hepatitis C (HCV) has an insidious onset with jaundice, fatigue, abdominal pain, nausea, and vomiting. It may cause mild to moderate illness, but chronicity is common, progressing to cirrhosis and liver failure. WHO estimates there are 170–180 million persons

chronically infected with HCV and 3–4 million newly infected globally each year. The CDC estimates that 3.2 million Americans are chronically infected with HCV, with 8000–10,000 resulting deaths per annum, and HCV is the main cause of liver transplants. HCV is transmitted most commonly in blood products, but also among injecting drug users (90 percent of intravenous drug users were HCV-positive in a Vancouver study in 1998), and is also a risk for health workers. The disease may also occur in dialysis centers and other medical situations. Person-to-person spread is unclear. Prevention of transmission includes routine testing of blood donations, antiviral treatment of blood products, needle exchange programs, and hygiene. The WHO in 1998 declared hepatitis prevention as a major public health crisis, stressing that this "silent epidemic" is being neglected and that screening of blood products is vital to reduce transmission of this disease as for HIV.

It is a major cause of liver cirrhosis, end-stage liver disease, and hepatocellular carcinoma. The virus is primarily transmitted parenterally. No immunization is available at present; however, research is currently directed at vaccine development. Interferon and ribavirin combination therapy is not curative, but may reduce symptoms and prevent HCV-associated cancers. Partly due to the virus's genetic diversity, it evades the host immune response and it has been difficult to develop vaccines.

Significant advances have been made in the treatment of chronic hepatitis C virus infection. Currently, the combination of interferon-alpha and ribavirin is the standard treatment for chronic hepatitis C virus infection, and leads to long-term eradication of the virus in approximately 54 percent of people. Treatment is expensive and has significant adverse effects. Prevention of transmission is primarily addressed to intravenous drug users. Developing countries have high levels of this a disease and very little in the way of resources to deal with it until a vaccine is developed.

Hepatitis D

Hepatitis D virus (HDV), also known as delta hepatitis, may be self-limiting or progress to chronic hepatitis. It is caused by a virus-like particle which requires HBV to reproduce. HDV infects cells along with HBV as a coinfection or in chronic carriers of HBV. HDV occurs worldwide in the same groups at risk for HBV. It also occurs in epidemics and is endemic in South America, Africa, and among drug users. Prevention is by measures similar to those for HBV. Management for HDV is by passive immunity with immunoglobulin for contacts and high-risk groups, and should include HBV vaccination as the diseases often coincide. There is currently no vaccine for HDV.

Hepatitis E

Hepatitis E virus has an epidemiologic and clinical course similar to that of HAV, and is a particle with an incubation period of 15–64 days. There is no evidence of a chronic form of HEV. One striking characteristic of HEV is its high mortality rate among pregnant women. Infection results from waterborne epidemics or as sporadic cases in areas with poor hygiene, spread via the oral–fecal route. It is a hazard in disaster situations with crowding and poor sanitary conditions. Prevention is by safe management of water supplies and sanitation. Treatment is supportive and symptom-directed; passive immunization is not helpful and no vaccine is currently available.

Haemophilus Influenzae Type B

Haemophilus influenzae type b (Hib) is a bacteria which causes meningitis and other serious infections in children. Before the introduction of effective vaccines, as many as 1 in 200 children developed invasive Hib infection. Two-thirds of these had Hib meningitis, with a case fatality rate of 2–5 percent. Long-term sequelae such as hearing impairment and neurologic deficits occurred in 15–30 percent of survivors.

The first Hib vaccine was licensed in 1985, based on capsular material from the bacteria. Extensive clinical trials in Finland demonstrated a high degree of efficacy, but less impressive results were in seen in postmarketing efficacy studies. By 1989, a conjugate vaccine based on an additional protein cell capsular factor capable of enhancing the immunologic response was introduced. Several conjugate vaccines are now available. This vaccine is now widely used in the industrialized countries and the 2006 WHO Advisory on Immunization Programs (SAGE) recommended wide-scale adoption of this important new vaccine.

The conjugate vaccines are now combined with DTaP as their schedule is simultaneous with that of the DTaP. Hib vaccine has been found to be cost-effective, despite being as costly as all the basic vaccines combined (i.e., DPT, OPV, MMR, and HBV). For this reason, its use thus far has been limited to industrialized countries. The vaccine is a valuable addition to the immunologic armamentarium. It showed dramatic results in local eradication of this serious early childhood infection in a number of European countries and a sharp reduction in the United States. The price of the vaccine has also fallen dramatically since the mid-1990s. As a result, in 1997, WHO recommended inclusion of Hib vaccine in routine immunization programs in developing countries.

Influenza

Influenza is an acute viral respiratory illness characterized by fever, headache, myalgia, prostration, and cough. Transmission is rapid by close contact with infected individuals and by airborne particles with an incubation period

of 1–5 days. It is generally mild and self-limited with recovery in 2–7 days. However, in certain population groups, such as the elderly and chronically ill, infection can lead to severe sequelae. Gastrointestinal symptoms commonly occur in children. During epidemics, mortality rates from respiratory diseases increase because of the large numbers of persons affected, although the case fatality rates are generally low.

Over the past century, influenza pandemics have occurred in 1889, 1918, 1957, and 1968, while epidemics are annual events. The influenza pandemic of 1918 caused millions of deaths among young adults, by some estimates killing more than had died in World War I. The influenza pandemic of 1918 killed nearly 50 million people worldwide and was characterized by an atypical mortality curve. Influenza usually mostly affects the very old and the very young. The principal group suffering from the 1918 pandemic was young men between the ages of 30 and 60 years, many in army training camps, as well as in the general population. Fear of recurrence of this pandemic led the CDC to launch a massive immunization program in the United States in 1976 to prevent swine flu (the virus was a strain antigenically similar to that of the 1918 pandemic influenza) from spreading from an isolated outbreak in an army camp. The effort was stopped after millions of persons were immunized with an urgently produced vaccine when serious reactions occurred (Guillain-Barré syndrome, a type of paralysis), and when no further cases of swine flu were seen. This demonstrated the difficulty of extrapolating scenarios from a historical experience (Box 4.7).

Box 4.7 High-Risk Groups Recommended for Annual Influenza Vaccination

1. Children between 6 months and 5 years of age.
2. Pregnant women.
3. Adults over 50 years of age.
4. Adults and children with chronic medical conditions.
5. Residents of long-term care facilities, such as nursing homes.
6. Persons in contact with high-risk individuals or populations.
7. Caregivers and contacts of infants and at-risk children.

Notes: Other groups should obtain medical advice regarding influenza risk and vaccination, such as immunosuppressed patients and those receiving chronic aspirin therapy, among others.

People with allergy to previous flu shot, eggs, or other vaccine components, or with history or risk for Guillain-Barré syndrome may not be candidates for vaccination; obtain medical advice.

Source: Centers for Disease Control. 2007. Prevention & Control of Influenza — Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR, Jul 13; 56(RR-06):1–54.

In recent years, concern has again arisen regarding the likelihood of virulent influenza pandemics. Of particular note is the influenza A H5N1 strain, known as avian influenza. WHO reports that from 2003 to October 2007, the number of confirmed human cases was 332 (204 deaths). Although relatively few human-to-human transmissions have been documented, this virus has rapidly spread among wild and domestic bird populations throughout Asia and much of the world. People who contact infected birds or poultry are at risk for severe disease, with over 60 percent case mortality. A minor mutation or genetic conjugation with a known human strain could result in a virus as deadly and contagious as the swine flu of 1918. It is estimated that up to 1.9 million people in the United States could die if such an outbreak occurs. Extensive international plans have been developed for intervention, should a virulent influenza pandemic occur. These include several vaccines with specificity to known virus strains. As many of the most devastating global communicable disease emergencies of recent centuries have been associated with highly pathogenic respiratory viruses, health systems and emergency plans must be prepared in the case of a pandemic. Active surveillance using sentinel chicken flocks now under surveillance for West Nile fever could be used to provide early warning of entry of the bird-borne disease into a specific region and help to trigger activation of response mechanisms.

Each year, epidemiologic services of the WHO and collaborating centers such as the CDC recommend which strains should be used in vaccine preparation for use among susceptible population groups. These vaccines are prepared with the current anticipated epidemic strains. The three main types of influenza (A, B, and C) have different epidemiologic characteristics. Type A and its subtypes, which are subject to antigenic shift, are associated with widespread epidemics and pandemics. Type B undergoes antigenic drift and is associated with less widespread epidemics. Influenza type C is even more localized.

Active immunization against the prevailing wild strain of influenza virus produces a 70–80 percent level of protection in high-risk groups. The benefits of annual immunization outweigh the costs, and it has proven to be effective in reducing cases of influenza and its secondary complications such as pneumonia and death from respiratory complications in high-risk groups.

Avian (H5N1) influenza is a threat to the world's population because of its potential to become a pandemic on the scale of the 1917–1918 flu epidemic. It is a bird-borne zoonotic disease so far affecting fowl such as chickens and turkeys contacted by infected wild fowl. Sensitive and robust surveillance measures are required to detect any evidence that the virus has changed and acquired the ability to transmit between humans. Surveillance is largely passive in relying on reports of infected wild and domestic

fowl and most important human cases. The major concern is for detection of human-to-human transmission and thus a threat to transform this disease into a local, regional, and world pandemic in a matter of months.

International efforts to improve national and local capacities in surveillance and response to this threat are vital to review the scale of the threat should the leap from animal-to-human to human-to-human transmission occur. An integral part of the pandemic planning response in the United Kingdom was the creation in 2005 of the U.K. National H5 Laboratory Network, capable of rapidly and accurately identifying potential human H5N1 infections in all regions of the United Kingdom and the Republic of Ireland.

The CDC relies on seven systems for national influenza surveillance, four of which operate year-round: 1) the WHO and the National Respiratory and Enteric Virus Surveillance System (NREVSS) collaborating laboratory systems; 2) the U.S. Influenza Sentinel Provider Surveillance System; 3) the 122 Cities Mortality Reporting System; and 4) a national surveillance system that records pediatric deaths associated with laboratory-confirmed influenza.

Pneumococcal Disease

Pneumococcal diseases, which are caused by *Streptococcus pneumoniae,* include pneumonia, meningitis, and otitis media. Together, these constitute the world's leading cause of vaccine-preventable child mortality; over 1 million children die from pneumococcal diseases each year. The 23 capsular types of pneumococci selected out of 83 known types of the organism for the polysaccharide vaccine (PPV23) are those responsible for 88 percent of pneumococcal pneumonia cases and 10–25 percent of all pneumonia cases in the United States. This vaccine has been found to be cost-effective for high-risk groups, including persons with chronic disease, HIV carriers, patients whose spleens were removed, the elderly, and those with immunosuppressive conditions. It should be included in preventive-oriented health programs, especially for long-term care of the chronically ill. In addition a 7-valent conjugate vaccine (PCV7) is now available for children under 2 years of age, the highest risk age group for pneumococcal disease mortality. The WHO and CDC recommend PCV7 for children under 2 years old and PPV23 for adults over 65 years of age. In addition, others at risk for respiratory disease or pneumococcal infection should be vaccinated.

Varicella (Chickenpox, Shingles, Herpes Zoster)

Varicella is an acute, generalized viral disease caused by the varicella zoster virus (VZV). Despite its reputation as an innocuous disease of childhood, varicella patients can be quite ill. A mild fever and characteristic generalized red rash last for a few hours, followed by vesicles occurring in successive crops over various areas of the body. Affected areas may include the membranes of the eyes, mouth, and respiratory tract. The disease may be so mild as to escape observation or may be quite severe, especially in adults. Death can occur from viral pneumonia in adults and sepsis or encephalitis in children. Neonates whose mothers develop the disease within 2 days of delivery are at increased risk, with a case fatality rate of up to 30 percent.

Long-term sequelae include herpes zoster or shingles with a severely painful, vesicular rash along the distribution of sensory nerves, which can last for months. Its occurrence increases with age and it is primarily seen in the elderly. It can, however, occur in immunocompromised children (especially those on cancer chemotherapy), AIDS patients, and others. Some 15 percent of a population will experience herpes zoster during their lifetimes. Reye syndrome is an increasingly rare but serious complication from varicella or influenza type b. It occurs in children and affects the liver and central nervous system. Congenital varicella syndrome with birth defects similar to congenital rubella syndrome has been identified, emphasizing the importance of effective immunization against VZV. Varicella vaccine is now recommended for routine immunization at age 12–18 months in the United States, with catch-up for nonimmunized children and adults, especially nonpregnant women of childbearing age. To maintain immunity in adolescence and adulthood, booster vaccinations after age 13 and again after age 50 are effective in those who have no history of VZV infection or evidence of immunity. Varicella vaccine is likely to be added to a "cocktail vaccine" containing DPT, polio (IPV), and Hib.

Meningococcal Meningitis

Meningococcal meningitis, caused by the bacterium *Neisseria meningitides,* is characterized by headache, fever, neck stiffness, delirium, coma, and/or convulsions. The incubation period is 2–10 days. It has a case fatality rate of 5–15 percent if treated early and adequately, but rises up to 50 percent in the absence of treatment. There are several important strains (A, B, C, X, Y, and Z). Serogroups A and C are the main causes of epidemics, with B causing sporadic cases and local outbreaks. Transmission is by direct contact and droplet spread.

Meningitis (group A) is common in sub-Saharan African countries, but epidemics have occurred worldwide. During epidemics, children, teenagers, and young adults are the most severely affected. In developed countries, outbreaks occur most frequently in military and college student populations. In 1997, meningococcal meningitis spread widely in the "meningitis belt" in Central Africa.

Epidemic control is achieved by mass chemoprophylaxis with antibiotics (e.g., rifampin or sulfa drugs) among case contacts, although the emergence of resistant strains is a concern. Vaccines against serotypes A and C (bivalent) or A, C, Y, and W-135 are available. Their use is effective in epidemic control and prevention institutions and military recruits, especially for A and C serogroups. Recommendations are to immunize using the tetravalent conjugate vaccine (MCV4) during preadolescent years, so immunity is established prior to residential education or military service.

VACCINE-PREVENTABLE DISEASES

VPDs are still among the leading causes of death in developing countries and many mid-level developing or transition countries are not using the full potential of vaccines currently available to protect their children. VPDs are a fundamental aspect of public health not only because of the success achieved in saving millions of lives, but in the enormous potential for future developments that may have equally valuable contribution to length and quality of life. However, the potential of even currently available vaccines is not yet fully realized and traditional practices in many countries are slow to adopt the newer vaccines, and their great life-saving capacity. The following table from WHO (Table 4.6) summarizes the scale of preventable deaths from VPDs.

ESSENTIALS OF AN IMMUNIZATION PROGRAM

Vaccination is one of the key modalities of primary prevention. Immunization is cost-effective and prevents wide-scale disease and death, with high levels of safety. Despite the general consensus in public health regarding the central role of vaccination, there are many areas of controversy and unfulfilled expectations.

A vaccination program should aim at 95 percent or higher coverage at appropriate times, including infants, schoolchildren, and adults. Immunization policy should be adapted from current international standards applying the best available program to national circumstances and financial capacities (Box 4.8). Public health personnel with expertise in VPD control are needed to advise ministries of health and the practicing pediatric community on current issues in vaccination and to monitor implementation and evolution of control programs. Controversies and changing views are common to immunization policy, so that discussions must be conducted on a continuing basis. Policy should be under continuing review by a government-appointed national immunization advisory committee, including professionals from public health, academia, immunology, laboratory sciences, economics, and relevant clinical fields.

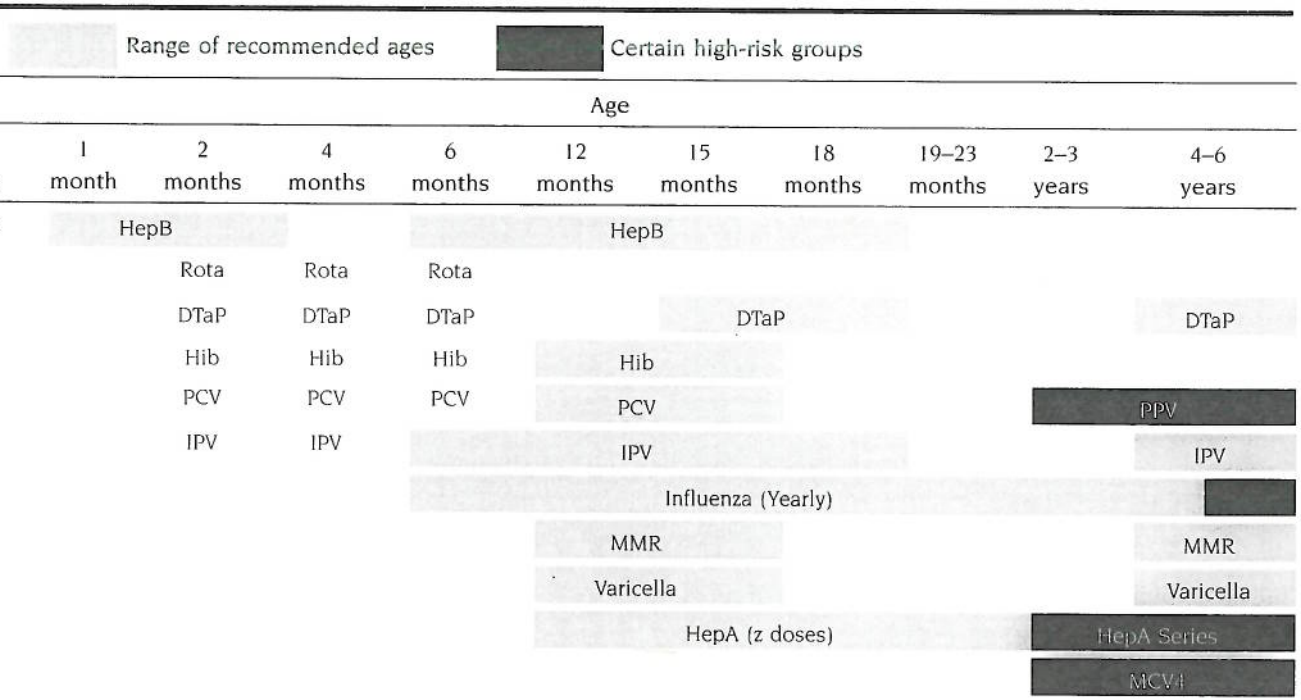
Vaccine supply should be adequate and continuous. Supplies should be ordered from known manufacturers meeting international standards of good manufacturing

TABLE 4.6 Estimated Number of Deaths in 2002 from Vaccine-Preventable Diseases (VPDs) Among Children <5 Years in 2002–2004. Diphtheria-Tetanus-Pertussis DTP Vaccine Coverage and Numbers of Unreached Infants and Incompletely Vaccinated Infants by WHO Region

WHO region	No. of deaths	% coverage with 1 dose of DTP	No. of unreached infants*	% coverage with 3 doses of DTP	No. of incompletely vaccinated infants†
African	1,113,000	78	5,607,000	66	3,048,000
American	44,000	96	562,000	92	659,000
Eastern Mediterranean	353,000	86	1,948,000	78	1,186,000
European	32,000	96	458,000	94	158,000
South East Asian	757,000	77	8,082,000	69	2,959,000
Western Pacific	251,000	96	1,051,000	90	1,302,000
Total	**2,550,000**	**86**	**17,708,000**	**78**	**9,312,000**

*Number of surviving infants who did not receive 1 dose of DTP, calculated on the basis of WHO/UNICEF estimates of vaccination coverage with 1 dose of DTP and estimates of surviving infants from *World Population Prospects: The 2004 Revision*.
†Number of surviving infants who did not receive 3 doses of DTP; unvaccinated infants were excluded.
World Health Organization Annual Report.

Box 4.8 Recommended Childhood Immunization Schedule, for Persons Aged 0–6, United States, 2006



This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2007, for children aged 0 through 6 years. Additional information is available at www.cdc.gov/vaccines/recs/schedules. Any dose not administered at the recommended age should be administered at any subsequent visit, when indicated and feasible. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and other components of the vaccine are not contraindicated and if approved by the Food and Drug Administration for that dose of the series. Providers should consult the respective Advisory Committee on Immunization Practices statement for detailed recommendations, including for high-risk conditions: http://www.cdc.gov/vaccines/pubs/ACIP-list.htm. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at www.vaers.hhs.gov or by telephone, 800–822–7967.

Source: Centers for Disease Control. 2008. Recommended Childhood and Adolescent Immunization Schedule — United States, Jan 6; 54(52):Q1–Q4.

Note: [a]OPV, Oral polio vaccine; IPV, inactivated polio vaccine; DPT or DPaT, diphtheria, pertussis, tetanus; preferably the acellular preparation (DTaP) and tetanus toxoid (DPT4 can be given at age 12 months if 6 months has elapsed since previous DPT); Td, diphtheria and tetanus; MMR, measles, mumps, rubella; Hep B, hepatitis B; Hib, *Haemophilus influenzae* type b; Var, varicella zoster virus; RV, rotavirus; #, for those who are not immunized in infancy.

[b]During 1999, the recommendation for poliovirus was changed to three doses of IPV in infancy.

practice. All batches should be tested for safety and efficacy prior to release for use. There should be an adequate and continuously monitored cold chain to protect against high temperatures for heat-labile vaccines, sera, and other active biological preparations. The cold chain should include all stages of storage, transport, and maintenance at the site of usage. Only disposable syringes should be used in vaccination programs to prevent any possible transmission of blood-borne infection.

A vaccination program depends on a readily available service with no barriers or unnecessary prerequisites, free to parents or with a minimum fee, to administer vaccines in disposable syringes by properly trained individuals using patient-oriented and community-oriented approaches. Ongoing education and training on current immunization practices are needed. Incentive payments by insuring agency or managed care systems promote complete, on-time coverage. All clinical encounters should be used to screen, immunize, and educate parents/guardians.

Contraindications to vaccination are very few; vaccines may be given even during mild illness with or without fever, during antibiotic therapy, during convalescence from illness, following recent exposure to an infectious disease, and to persons having a history of mild/moderate local reactions, convulsions, or family history of sudden infant death syndrome (SIDS). Simultaneous administration of vaccines and vaccine "cocktails" reduces the number of visits and thereby improves coverage; there are no known interferences between vaccine antigens.

Accurate, complete recording with computerization of records and automatic reminders helps promote compliance, as does co-scheduling of immunization appointments with other services. Adverse events should be reported promptly, accurately, and completely. A tracking system should operate with reminders of upcoming or overdue immunizations; use mail, telephone, and home visits, especially for high-risk families, with semiannual audits to assess coverage and review patient records in the population served to determine the percentage of children covered by their second birthday. Tracking should identify children needing completion of the immunization schedule and assess the quality of documentation. It is important to maintain up-to-date, easily retrievable medical protocols where vaccines are administered, noting vaccine dosage, contraindications, and management of adverse events.

All health care providers and managers should be trained in education, promotion, and management of immunization policy. Health education should target parents as well as the general public. Monitoring of vaccines used and children immunized, individually and by category of vaccination, can be facilitated by computerization of immunization records, or regular manual review of child care records. Where immunization is done by physicians in private practice, as in the United States, determination of coverage is by periodic surveys.

Regulation of Vaccines

Inspection of vaccines for safety, purity, potency, and standards is part of the regulatory function. Vaccines are defined as biological products and are therefore subject to regulation by national health authorities. In the United States, this comes under the legislative authority of the Public Health Service Act, as well as the Food, Drug and Cosmetics Act, with applicable regulations in the Code of Federal Regulations. The federal agency empowered to carry out this regulatory function is the Center for Drugs and Biologics of the Federal Food and Drug Administration.

Litigation regarding adverse effects of vaccines led to inflation of legal costs and efforts to limit court settlements. The U.S. federal government enacted the Child Vaccine Injury Act of 1988, establishing the National Vaccine Injury Compensation Program (VICP). This legislation requires providers to document vaccines given and to report on complications or reactions. It was intended to pay benefits to persons injured by vaccines faster and by means of a less expensive procedure than a civil suit for resolving claims. Using this no-fault system, petitioners do not need to prove that manufacturers or vaccine givers were at fault. They must only prove that the vaccine is related to the injury in order to receive compensation. The vaccines covered by this legislation include Hib, HAV, HBV, HPV, influenza, meningococcal, pneumococcal, rotavirus, VZV, DTaP/TdaP, MMR, OPV, and IPV.

Newly recommended vaccines for children and adolescents have nearly doubled in number since 2000, and the cost of fully vaccinating a child has increased dramatically in the past decade. Funding of the extensive recommended schedule is a problem in all countries where this is provided as a public health service or where it is covered by health insurance. In the United States, with a lack of health insurance for some 15 percent of the population and low levels of coverage for another 15 percent, lack of coverage for immunization is a significant problem. Many of the poorest children are covered under the Women, Infants, and Children nutrition support program, but others in the working poor population may lack access. This is an issue of debate in current political struggles to provide universal coverage for children.

Vaccine Development

Development of vaccines from Jenner in the eighteenth century to the advent of recombinant hepatitis B vaccine in 1987, and of vaccines for acellular pertussis, varicella, hepatitis A, and rotavirus in the 1990s, has provided one of the pillars of public health and led to enormous saving of human life. Vaccines for viral infections in humans for HIV, respiratory syncytial virus, Epstein-Barr virus, dengue fever, and hantavirus are under intense research

with genetic approaches using recombinant techniques. The potential for the future of vaccines will be greatly influenced by scientific advances in genetic and molecular technology, with potential for development of vaccines attached to bacteria or protein in plants, which may be given in combination against an increasing range of organisms or toxins.

Recombinant DNA technology has revolutionized basic and biomedical research since the 1970s. The industry of biotechnology has produced important diagnostic tests, such as for HIV, with great potential for vaccine development. Traditional whole organism vaccines, alive or killed, may contain toxic products that may cause mild to severe reactions. Subunit vaccines are prepared from components of a whole organism. This avoids the use of live organisms that can cause the disease or create toxic products which cause reactions. Subunit vaccines traditionally prepared by inactivation of partially purified toxins are costly, difficult to prepare, and weakly immunogenic. Recombinant techniques are an important development for production of new whole cell or subunit vaccines that are safe, inexpensive, and more productive of antibodies than other approaches. Their potential contribution to the future of immunology is enormous.

Molecular biology and genetic engineering have made it feasible to create new, improved, and less costly vaccines. New vaccines should be inexpensive, easily administered, capable of being stored and transported without refrigeration, and given orally. The search for inexpensive and effective vaccines for groups of viruses causing diarrheal diseases led to development of the rotavirus vaccine. Some "edible" research focuses on the genetic programming of plants to produce vaccines and DNA. Vaccine manufacturers, who spend huge sums of money and years of research on new products, tend to work on those which will bring great financial rewards for the company and are critical to the local health care community. This has led to less effort being made in developing vaccines for diseases such as malaria which affect primarily the developing world. Industry plays a crucial role for continued progress in the field; therefore, work must be done to establish incentives for research, development, and application of vaccine technology from a global perspective.

CONTROL/ERADICATION OF INFECTIOUS DISEASES

Since the eradication of smallpox, much attention has focused on the possibility of similarly eradicating other diseases, and a list of potential candidates has emerged. Some of these have been abandoned because of practical difficulties with current technology. Diseases that have been under discussion for eradication have included measles, polio, and some tropical diseases, such as malaria and dracunculiasis. *Eradication* is defined as the achievement of a situation whereby no further cases of a disease occur anywhere and continued control measures are unnecessary. Reducing epidemics of infectious diseases, through control and eradication in selected areas or target groups, can in certain instances achieve eradication of the disease. Local eradication can be achieved where domestic circulation of an organism is interrupted with cases occurring from importation only. This requires a strong, sustained immunization program with adaptation to meet needs of importation of carriers and changing epidemiologic patterns.

Smallpox

Smallpox was one of the major pandemic diseases of the Middle Ages and its recorded history goes back to antiquity. Prevention of smallpox was discussed in ancient China by Ho Kung (circa 320 CE), and inoculation against the disease was practiced there from the eleventh century CE. Prevention was carried out by nasal inhalation of powdered dried smallpox scabs. Exposure of children to smallpox when the mortality rate was lowest assumed a weakened form of the disease, and it was observed that a person could only have smallpox once in a lifetime. Isolation and quarantine were widely practiced in Europe during the sixteenth and seventeenth centuries.

Variolation was the practice of inoculating youngsters with material from scabs of pustules from mild cases of smallpox in the hope that they would develop a mild form of the disease. Although this practice was associated with substantial mortality, it was widely adopted because mortality from variolation was well below that of smallpox acquired during epidemics. Introduced into England in 1721 (see Chapter 1) it was commonly practiced as a lucrative medical specialty during the eighteenth century. In the 1720s, variolation was also introduced into the American colonies, Russia, and subsequently Sweden and Denmark.

Despite all efforts, in the early eighteenth century, smallpox was a leading cause of death in all age groups. Toward the end of the eighteenth century, an estimated 400,000 persons died annually from smallpox in Europe. Vaccination, or the use of cowpox vaccinia virus to protect against smallpox, was initiated late in the eighteenth century. In 1774, a cattle breeder in Yorkshire, England, inoculated his wife and two children with cowpox to protect them during a smallpox epidemic. In 1796, Edward Jenner, an English rural general practitioner, experimented with inoculation from a milkmaid's cowpox pustule to a healthy youngster, who subsequently proved resistant to smallpox by variolation (see Chapter 1). Vaccination, the deliberate inoculation of cowpox material, was slow to be adopted universally, but by 1801, over 100,000 persons in England were vaccinated. Vaccination gathered support in the nineteenth century in military establishments and in some countries that adopted it universally.

Opposition to vaccination remained strong for nearly a century based on religious grounds, observed failures of vaccination to give lifelong immunity, and because it was seen as an infringement of the state on the rights of the individual. Often the protest was led by medical variolationists whose medical practice and large incomes were threatened by the mass movement to vaccination. Resistance was also offered by "sanitarians" who opposed the germ theory and thought cleanliness was the best method of prevention. Universal vaccination was increasingly adopted in Europe and America in the early nineteenth century and eradication of smallpox in developed countries was achieved by the mid-twentieth century.

In 1958, the Soviet Union proposed to the World Health Assembly a program to eradicate smallpox internationally and subsequently donated 140 million doses of vaccine per year as part of the 250 million needed to promote vaccination of at least 80 percent of the world population. In 1967, WHO adopted a target for the eradication of smallpox. The program included a massive increase in coverage to reduce the circulation of the virus through person-to-person contact. Where smallpox was endemic, with a substantial number of unvaccinated persons, the aim of the mass vaccination phase was 80 percent coverage.

Increasing vaccination coverage in developing countries reduced the disease to periodic and increasingly localized outbreaks. In 1967, 33 countries were considered endemic for smallpox, and another 11 experienced importation of cases. By 1970, the number of endemic countries was down to 17, and by 1973 only 6 countries were still endemic, including India, Pakistan, Bangladesh, and Nepal. In these countries, a new strategy was needed, based on a search for cases and vaccination of all contacts, working with a case incidence below 5 per 100,000. The program then moved into the consolidation phase, with emphasis on vaccination of newborns and new arrivals. Surveillance and case detection were improved with case contact or risk group vaccination. The maintenance phase began when surveillance and reporting were switched to the national or regional health service with intensive follow-up of any suspect case. The mass epidemic era had been controlled by mass vaccination, reducing the total burden of the disease, but eradication required the isolation of individual cases with vaccination of potential contacts.

Technical innovations greatly eased the problems associated with mass vaccination worldwide. During the 1920s, there was wide variation in sources of smallpox vaccine. In the 1930s, efforts to standardize and further attenuate the strains used reduced complication rates from vaccinations. The development of lyophilization (freeze-drying) of the vaccine in England in the 1950s made a heat-stable vaccine that could be effective in tropical field conditions in developing countries. The invention of the bifurcated needle (Rubin, 1961) allowed for easier and more widespread vaccination by lesser trained personnel in remote areas. The net result of these innovations was increased world coverage and a reduction in the spread of the disease. Smallpox became more and more confined by increasing herd immunity, thus allowing transition to the phase of monitoring and isolation of individual cases.

In 1977 the last case of smallpox was identified in Somalia, and in 1980 the WHO declared the disease eradicated. No subsequent cases have been found except for several associated with a laboratory accident in the United Kingdom in 1978. The cost of the smallpox eradication program was $112 million or $8 million per year. Worldwide savings are estimated at $1 billion annually. This monumental public health achievement set the precedent for eradication of other infectious diseases. The World Health Assembly recommended destruction of the last two remaining stocks of the smallpox virus in Atlanta and Moscow in 1999. This was delayed in 1999 due to concern that illegal stocks may be held by some states or terrorists for potential use as weapons of mass destruction, concern regarding the appearance of monkeypox, and a wish to use the virus for further research. Today, virus stocks are handled only in select laboratories with high security. In addition, emergency plans have been developed, including the immunization of key health workers to limit the extent of a bioterror-engendered epidemic.

Eradication of Poliomyelitis

In 1988, the WHO established a target of eradication of poliomyelitis. Although polio epidemics continue, largely in countries with limited access to public health, the burden of disease worldwide has been greatly reduced. At the initiation of the polio eradication campaign, 350,000 cases of childhood paralysis were attributed to polio in 125 countries. By 2006, this number was reduced to 68,000. Only four countries have never achieved wild-poliovirus interruption: Afghanistan, India, Nigeria, and Pakistan. Support from member countries and international agencies such as UNICEF and Rotary International has led to wide-scale increases in immunization coverage throughout the world. The WHO promotes use of OPV as part of routine infant immunization on National Immunization Days (NIDs). This strategy has been successful in the Americas, Europe, and China, but several countries remain problematic.

Eradication of wild poliomyelitis will require flexibility in vaccination strategies and may require the combined approach, using OPV and IPV, as adopted in the United States in 1997 to prevent vaccine-associated clinical cases. Currently, IPV is largely used only in countries where interruption has occurred. Lack of intestinal immunity may be a risk for imported polio though. The combination of OPV and IPV may be needed where enteric disease is common and leads to interference in OPV uptake, especially in tropical areas where endemic poliovirus and diarrheal diseases are still found. In 2004, polio made a resurgence in Nigeria and in 2005 in a number of countries thought to be under

control. The use of OPV has been put in doubt by recent decisions in the industrialized countries to follow the U.S. example of IPV only. The developing countries will need to rely on OPV in the coming years because of high cost and limited supply of IPV.

Other Candidates for Eradication

Success in the eradication of smallpox, followed by increasing control and the prospect of eradication of poliomyelitis, as well as other VPDs, has led to optimism in identifying other diseases which could potentially be eradicated or eliminated as public health problems. A list of potential candidates has been identified. Some of these have since been abandoned due to practical and technological difficulties. Diseases that have been under discussion for eradication have included measles, TB, and tropical diseases such as malaria and dracunculiasis.

Eradication of malaria was thought to be possible in the 1950s when major gains were seen in malaria control by aggressive case environmental control, case finding, and management. However, lack of sustained vector control and an effective vaccine has prevented global eradication. Malaria control suffered serious setbacks because of failure in political resolve and capacity to continue support needed for necessary programs. In the 1960s and 1970s, control efforts were not sustained in many countries, and a dreadful comeback of the disease occurred in Africa and Asia in the 1980s. The emergence of mosquitoes resistant to insecticides, and parasite strains of the parasite resistant to antimalarial drugs have made control even more difficult and expensive.

Renewed efforts in malaria control may require new approaches. Use of community health workers (CHWs) in small villages in highly endemic regions of Colombia resulted in a major drop in malaria mortality during the 1990s. The CHWs investigate suspect cases by taking clinical histories and blood smears. A presumptive diagnosis is made clinically or by local examination of blood smears. Therapy is instituted rapidly, and the patient is followed. Quality control monitoring shows high levels of accuracy in reading of slides compared to professional laboratories. Use of DDT-impregnated bed nets has become a major method of prevention. The banning of DDT completely since the 1960s is now seen as an overreaction to legitimate concerns for its widespread use, but vector control remains a key element of malaria control, and DDT has a role in this. Since 2006, WHO has recommended use of DDT-impregnated bed nets and limited uses of DDT for protecting homes to reduce the risk of infection of children especially.

In the late 1970s, there was widespread discussion in the literature of the potential for eradication of measles and TB. Measles eradication was set back as breakthrough epidemics occurred in the United States, Canada, and many other countries during the 1980s and early 1990s, but regional eradication was achieved combining the two-dose policy with catch-up campaigns for older children or in National Immunization Days, as in the Caribbean countries.

Tuberculosis has also increased in the United States and several European countries for the first time in many decades. Unrealistic expectations can lead to inappropriate assessments and policy when confounding factors alter the epidemiologic course of events. Such is the case with TB, where control and eradication have receded from the picture. This deadly disease has returned to developed countries, partly in association with the HIV infection and multidrug-resistant strains, as well as homelessness, rising prison populations, poverty, and other deleterious social conditions. Directly observed therapy is an important recent breakthrough, more effective in use of available technology, and it will play a major role in TB control in the twenty-first century.

Future Candidates for Eradication

A decade after the eradication of smallpox was achieved, the International Task Force for Disease Eradication (ITFDE) was established to systematically evaluate the potential for global eradicability of candidate diseases. Its goals were to identify specific barriers to the eradication of these diseases that might be surmountable and to promote eradication efforts (Box 4.9).

The subject of eradication versus control of infectious diseases is of central public health importance as technology expands the armamentarium of immunization and vector control into the twenty-first century. The control of epidemics, followed by interruption of transmission and ultimately eradication, will save countless lives and prevent serious damage to children throughout the world. The smallpox achievement, momentous in itself, points to the potential for the eradication of other deadly diseases. The skillful use of existing and new technology is an important priority in the New Public Health. Flexibility and adaptability are as vital as resources and personnel.

Selecting diseases for eradication is not purely a professional issue of resources such as vaccines and manpower, organization, and financing. It is also a matter of political will and perception of the burden of disease. There will be many controversies. The CDC published criteria for selection of disease for eradication as shown in Table 4.7.

The WHO, in a 1998 review of health targets in the field of infectious disease control for the twenty-first century, selected the following targets: eradication of Chagas' disease by 2010; eradication of neonatal tetanus by 2010; eradication of leprosy by 2010; eradication of measles by 2020; eradication of trachoma by 2020; and reversing the current trend of increasing tuberculosis and HIV/AIDS. Many of these campaigns have achieved interim goals. Although primary targets for eradication, such as polio, have proven problematic, the coming years appear to be a horizon for

Box 4.9 Criteria for Assessing Eradicability of Diseases, International Task Force for Disease Eradication (ITFDE)

1. Scientific feasibility
   a. Epidemiologic vulnerability; lack of nonhuman reservoir, ease of spread, no natural immunity, relapse potential;
   b. Effective practical intervention available; vaccine or other primary preventive or curative treatment, or vectoricide that is safe, inexpensive, long-lasting, and easily used in the field;
   c. Demonstrated feasibility of elimination in specific locations, such as an island or other geographic unit.
2. Political will/popular support
   a. Perceived burden of the disease; morbidity, mortality, disability, and costs of care in developed and developing countries;
   b. Expected cost of eradication;
   c. Synergy of implementation with other programs;
   d. Reasons for eradication versus control.

Source: World Health Organization. 1992. Update International Task Force for Disease Eradication 1991. *Morbidity and Mortality Weekly Report*, 41:40–42.

breakthroughs and elimination of many preventable diseases. A review of onchocerciasis eradication efforts in 2007 concluded that eradication of the disease could be achieved in the Americas but not yet in Africa, but that achievements to date should be preserved by cooperative efforts of WHO, the World Bank, UNDP, and others. The struggle to eliminate and potentially eradicate important diseases, such as was achieved with smallpox, will require many years of strong political and funding support as well as a strong cadre of public health workforce with new scientific breakthroughs (such as malaria and HIV vaccines), but the movement even when partially successful is saving millions of lives and improving quality of life for many more.

Tuberculosis

Tuberculosis (TB) is caused by a group of organisms including *Mycobacterium tuberculosis* in humans and *M. bovis* in cattle. The disease is primarily found in humans, but it is also a disease of cattle and occasionally other primates in certain regions of the world. It is transmitted via airborne droplet nuclei from persons with pulmonary or laryngeal TB during coughing, sneezing, talking, or singing. The initial infection may go unnoticed, but tuberculin sensitivity

TABLE 4.7 Potential Disease Candidates for Control and Eradication, 1998

Organism	Control — Elimination as a public health problem	Eradicable — Regional/global
Bacterial diseases	Pertussis Neonatal tetanus Congenital syphilis Trachoma Tuberculosis Leprosy	Diphtheria *Haemophilus influenzae* type b
Viral disease	Hepatitis B Hepatitis A Yellow fever Rabies Japanese encephalitis	Poliomyelitis Measles Rubella Mumps
Parasitic disease	Malaria Chagas' disease Helminthic infestation Schistosomiasis Leishmaniasis, visceral	Echinococcus Teniasis
Noninfectious disease	Lead poisoning Silicosis Protein energy malnutrition Micronutrient malnutrition Iodine deficiency Vitamin A deficiency Folic acid deficiency Iron deficiency	

Source: Goodman, R. A., Foster, K. L., Trowbridge, F. L., Figuero, J. P. (eds.). 1998. Global Disease Elimination and Eradication as Public Health Strategies: Proceedings of a Conference Held in Atlanta, Georgia, USA, 23–25 February 1998. *Bulletin of the World Health Organization*, 76 Supplement 2 1–161.

appears within a few weeks. About 95 percent of those infected enter a latent phase with a lifelong risk of reactivation. Approximately 5 percent go from initial infection to pulmonary TB. Less commonly, the infection develops as extrapulmonary TB, involving meninges, lymph nodes, pleura, pericardium, bones, kidneys, or other organs.

Untreated, about half of the patients with active TB will die of the disease within 2 years, but modern chemotherapy almost always results in a cure. Pulmonary TB symptoms include cough and weight loss, with clinical findings on chest examination and confirmation by findings of tubercle bacilli in stained smears of sputum and, if possible, growth of the organism on culture media, and changes in the chest x-ray. Tuberculosis affects people in their adult working years, with 80–90 percent of cases in persons between the ages of 15 and 49. Its devastating effects on the workforce and economic development contribute to a high cost-effectiveness for TB control.

Nearly one-third of the world's population is infected with tuberculosis. In 2005, there were over 8.8 million new cases and nearly 1.6 million deaths. During 2005, new cases of TB included 3.0 million in southeast Asia and 2.5 million in Africa, where HIV disease has become the leading comorbidity and risk for TB mortality. Between 1990 and 1999, WHO estimates there were 88 million new cases of TB, of which 8 million cases were in association with HIV infection. During the 1990s, an estimated 30 million persons died of TB, including 2.9 million with HIV infection. The 2008 Global Tuberculosis Control Report reported 9.2 million new cases in 2006 including 400,000 new cases of multidrug-resistant TB; approximately 1.5 million died of TB in 2006.

A new and dangerous period for TB resurgence has resulted from parallel epidemiologic events: first, the advent of HIV infection and, second, the occurrence of multidrug-resistant TB (MDRTB); that is, organisms resistant at least to both isoniazid (INH) and rifampin, two mainstays of TB treatment. MDRTB can have a case fatality rate as high as 70 percent. HIV reduces cellular immunity so that people with latent TB have a high risk of activation of the disease. It is estimated that HIV-negative persons have a 5–10 percent lifetime risk of TB; HIV-positive people have a risk of 10 percent per year of developing clinical tuberculosis (Box 4.10).

Drug resistance, the long period of treatment, and the socioeconomic profile of most TB patients combine to require a new approach to therapy. Directly observed treatment, short-course (DOTS), has shown itself to be highly effective with patients in poor self-care settings, such as the homeless, drug users, and those with AIDS. The strategy of DOTS uses community health workers to visit the patient and observes him or her taking the various medications, providing both incentive, support, and moral coercion to complete the needed 6–8 month therapy. DOTs has been shown to cure up to 95 percent of cases, at a cost of as little as $11 over the period of treatment per patient. It is one of the few hopes of containing the current TB pandemic.

Box 4.10 Principal Issues of Control of Tuberculosis

- Identifying persons with clinically active TB;
- Diagnostic methods — clinical suspicion, sputum smear for bacteriologic examination, tuberculin skin testing, chest radiograph;
- Case finding and investigation programs in high-risk groups;
- Contact investigation;
- Isolation techniques only during initial therapy;
- Treatment, mainly ambulatory, of persons with clinically active TB;
- Investigation and treatment of contacts;
- Directly observed treatment, short-course (DOTS), where compliance is suspect;
- Environmental control in treatment settings to reduce droplet infection;
- Educate health care providers on suspicion of TB and investigation of suspects.

In 2006, WHO rededicated itself to TB control with the "Stop TB Strategy" for control of tuberculosis over the next decade. The plan calls for new guidelines for control, new aid funds for developing countries, and enlistment of NGOs to assist in the fight. The new guidelines stress short-term chemotherapy in well-managed programs of DOTS, stressing strict compliance with therapy for infectious cases with a goal of an 85 percent cure rate. Even under adverse conditions, DOTS produces excellent results. It is one of the most cost-effective health interventions combining public health and clinical medical approaches. Primary goals of the Stop TB Strategy are to reduce TB incidence and mortality by 50 percent by 2015, compared to 1990, and to eliminate TB as a public health problem by the year 2050 (Figure 4.3).

Tuberculosis incidence in the United States decreased steadily until 1985, increased in 1990, and has declined again since (Figure 4.4). From 1986 to 1992, there was an excess of 51,600 cases over the expected rate if the previous decline in case incidence had continued. This rise was largely due to the HIV/AIDS epidemic and the emergence of MDRTB, but also greater concentration among immigrants from areas of higher TB incidence, drug abusers, the homeless, and those with limited access to health care. This is particularly true in New York City, where MDRTB has appeared in outbreaks among prison inmates and hospital staff.

TB incidence in the United States declined due to stronger TB control programs that promptly identify persons with TB and ensure completion of appropriate therapy. Aggressive staff training, outreach, and case management approaches were vital to this success. Concern over rising rates among recent immigrants and the continued challenge of HIV/AIDS and coincidental transmission of hepatitis A, B, and C among drug users and marginal population groups show that continued support for TB control is needed.

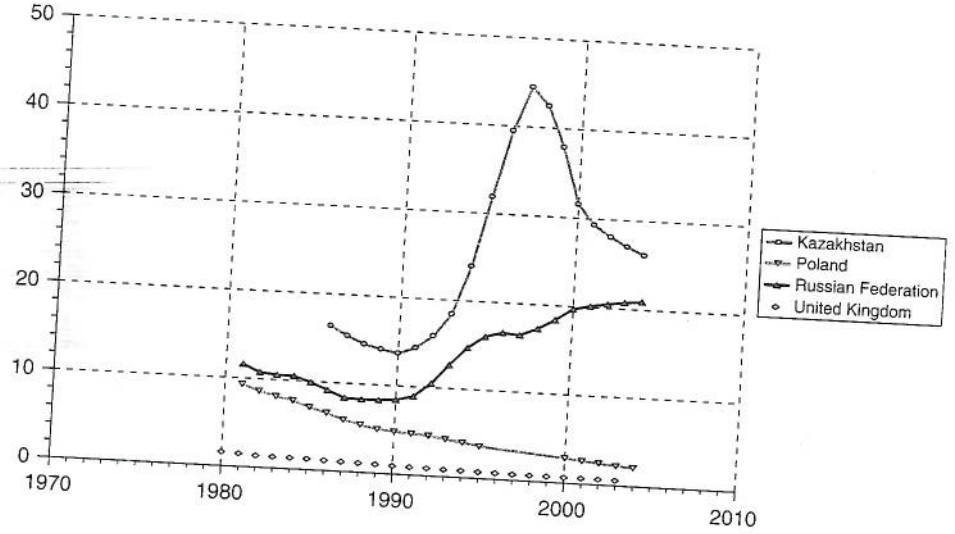


FIGURE 4.3 SDR for Tuberculosis in Poland, Kazakhstan, Russia, and the UK. Note: Standardized Death Rates per 100,000 population. Source: Health for All database WHO European Region, November 2007, http://www.euro.who.int/hfadb [accessed May 24, 2008]

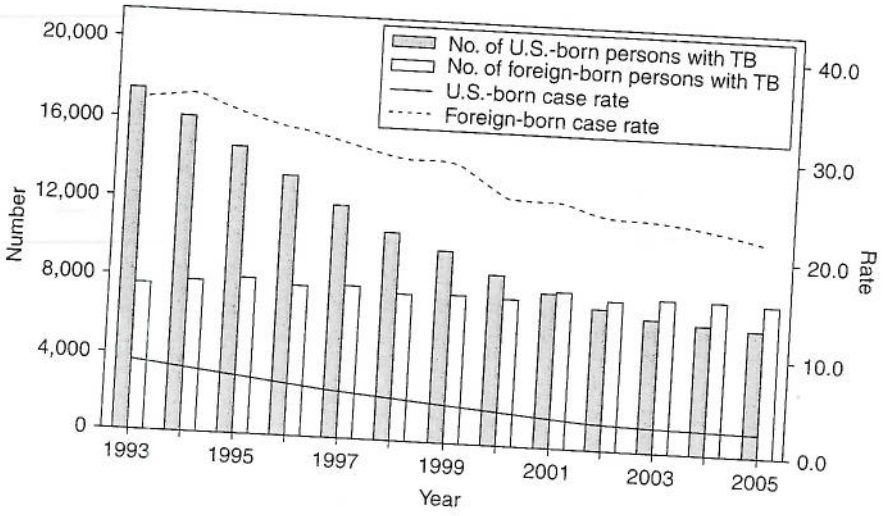


FIGURE 4.4 Tuberculosis numbers and rates, by origin of birth and year, United States, 1993–2005. Source: CDC, Reported Tuberculosis in the United States, 2005, Atlanta, GA: U.S. DHHS, CDC, 2006, http://www.cdc.gov/tb/surv/surv2005/PDF/TBSurvFULLReport.pdf [accessed June 2, 2008]

Bacille Calmette-Guérin (BCG) is an attenuated strain of the tubercle bacillus used widely as a vaccination to prevent TB, especially in high-incidence areas. It induces tuberculin sensitivity or an antigen–antibody reaction in which antibodies produced may be somewhat protective against the tubercle bacillus in 90 percent of vaccinees. Although the support for its general use is contradictory, there is evidence from case–control and contact studies of positive protection against TB meningitis and disseminated TB in children under the age of 5. In some developed, low-incidence countries, it is not used routinely but selectively. It may also be used in asymptomatic HIV-positive persons or other high-risk groups.

The BCG vaccine for tuberculosis remains controversial. While used widely internationally, in the United States and other industrialized countries, it is thought to hinder rather than help in the fight against TB. This concern is based on the usefulness of tuberculin testing for diagnosis of the disease. Where BCG has been administered, the diagnostic value of tuberculin testing is reduced, especially in the period soon after the BCG is used. Studies showing equivocal benefit of BCG in preventing tuberculosis have added to the controversy. While those in the field in the United States continue to oppose the use of BCG, internationally it is still felt to be of benefit in preventing TB, primarily in children. Currently, the WHO recommends use of a single dose of BCG as close to birth as possible as part of the EPI.

A 1994 meta-analysis of the literature of BCG carried out by the Technology Assessment Group at Harvard School of Public Health concluded that on average, BCG vaccine significantly reduces the risk of TB by 50 percent. Protection is observed across many populations, study designs, and forms of TB. Age at vaccination did not enhance BCG efficacy. Protection against tuberculosis death, meningitis, and disseminated disease is higher than for total TB cases,

although this result may reflect reduced error in disease classification rather than greater BCG efficacy.

Limitations of current chemotherapy and the only available vaccine, BCG, in the fight against TB make the continued search for new vaccines and therapeutics vital, possibly aided by new methods in design of vaccines and drugs. However, the struggle is now best fought by a combination of DOTS and DOTS plus (for multidrug-resistant strains) along with poverty alleviation and nutritional improvements in vulnerable population groups (Box 4.11).

In 1993, the WHO adopted a national case management strategy, DOTS to reduce the increasing global burden of TB, especially in developing countries. The five elements of the DOTS strategy are sustainable government commitment, quality assurance of sputum microscopy, standardized short-course treatment (including direct observation therapy), regular supply of drugs, and establishment of reporting and recording systems.

The goal of DOTS is to reduce TB morbidity and mortality and the chance of *Mycobacterium tuberculosis* developing resistance to primary treatment drugs. Target goals of TB control adopted in 1991 by the World Health Assembly include ≥70 percent detection rate of the estimated incidence of sputum-smear–positive pulmonary TB (PTB+) and ≥85 percent cure rate for newly detected PTB+ cases. The ≥85 percent cure rate was adopted on the basis of accumulated experience in Africa and certain districts of China.

Box 4.11 Control of Tuberculosis in Kazakhstan Using DOTS

To manage the increasing burden of TB in the country, in 1998 the Kazakhstan Ministry of Health adopted and implemented a new National Tuberculosis Program (NTP), whose objectives and target goals are in accord with the DOTS strategy. To implement the DOTS strategy in Kazakhstan, primary health care physicians and TB specialists received training in case-detection policy, and laboratories were equipped with binocular microscopes. Unfavorable treatment outcomes for new PTB+ cases were associated with alcohol abuse, homelessness, previous incarceration, unemployment, being male, and urban residence. The epidemic curve peaked in 1998 with a continuous decline since. Treatment of multidrug-resistant TB is more costly and complex, but has become an essential part of international TB work.

Sources: Centers for Disease Control. 2006. Progress toward tuberculosis control and determinants of treatment outcomes — Kazakhstan, 2000–2002. *Morbidity and Mortality Weekly Report*, 55 (SUP01):11–15.
World Health Organization. 2003. *Treatment of Tuberculosis: Guidelines for National Programs*. Geneva: World Health Organization (WHO/CDS/TB/2003.313).

Performance indicators in the DOTS program use the proportion detected of PTB+, which is the most infectious form of TB. PTB+ is associated with high mortality and is the most effective form of TB to use for bacteriologic monitoring of treatment progress. The proportion of newly detected PTB+ cases among the total number of adults with PTB reflects the proper application of diagnostic criteria. In countries with a medium or high TB burden, when necessary laboratory resources are available and sputum smears for microscopy are taken from TB patients, PTB+ accounts for >50 percent of all TB cases and >65 percent of new PTB cases in adults. Achieving a high (i.e., ≥85 percent) cure rate for PTB+ is a critical priority for TB-control programs. Failure to achieve this rate results in continued infectiousness and possible development of MDR TB, resistant to at least isoniazid and rifampin.

Tuberculosis control remains feasible with current medical and public health methods. Deterioration in its control should not lead to despair and passivity. The recent trend to successful control by DOTS despite the growing problem of MDRTB suggest that control and gradual reduction can be achieved by an activist, community outreach approach. The WHO in 2006 reaffirmed TB control as one of its major priorities, expressing grave concern that the MDR organism, now widely spread in countries of Asia, eastern Europe, and the former Soviet Union, may spread the disease much more widely. The disease constitutes one of the great challenges to public health.

Extremely drug-resistant TB, XMDR-TB, has become a central concern in addressing the current TB epidemic and is part of a WHO-led strategy in this field. The Millennium Development Goals include TB with specific targets endorsed by the Stop TB Partnership:

- 2005: detect at least 70 percent of new sputum smear-positive TB cases and cure at least 85 percent of these cases;
- by 2015: reduce prevalence of and death due to TB by 50 percent relative to 1990;
- by 2050: eliminate TB as a public health problem (<1 case per million population).

Streptococcal Diseases

Acute infectious diseases caused by group A streptococci include streptococcal sore throat, scarlet fever, puerperal fever, septicemia, erysipelas, cellulitis, mastoiditis, otitis media, pneumonia, peritonsillitis (quinsy), wound infections, toxic shock syndrome, and fasciitis, the "flesh eating bacteria." *Streptococcus pyogenes* group A includes some 80 serologically distinct types which vary in geographic location and clinical significance. Transmission is by droplet, person-to-person direct contact, or food infected by carriers. Important complications from a public health point of view include acute rheumatic fever and acute glomerulonephritis, but also skin infections and pneumonia.

Acute rheumatic fever (ARF) is a complication of strep A infection that has virtually disappeared from industrialized countries as a result of improved standards of living and antibiotic therapy. Mortality rates from rheumatic fever and rheumatic heart disease has declined steadily over the last 3 decades, largely due to increase in availability and use of antibiotics. In developing nations and lower socioeconomic areas where rheumatic fever is more prevalent, ARF is a major cause of death and disability in children and adolescents. However, outbreaks were recorded in the United States in 1985, and an increasing number of cases have been seen since 1990. In developing countries, rheumatic fever remains a serious public health problem affecting school-age children, particularly those in crowded living arrangements. Long-term sequelae include disease of the mitral and aortic heart valves, which require cardiac care and surgery for repair or replacement with artificial valves.

Acute glomerulonephritis is a reaction to toxins of the streptococcal infection in the kidney tissue. This can result in long-term kidney failure and the need for dialysis or kidney transplantation. This disease has become far less common in the industrialized countries, but remains a public health problem in developing countries.

Group B streptococci (GBS) are related organisms. They commonly colonize the reproductive tract of women of reproductive age, and are the leading cause of meningitis in newborn infants. As with other strains of beta-hemolytic streptococci, treatment with penicillin (or appropriate therapy for allergic patients) is effective. Women should be screened for GBS at 35–37 weeks of pregnancy and treated during labor and delivery. If screening tests are unavailable, the risk of infection is high; recommendations are to treat prophylactically.

The streptococcal diseases are controllable by early diagnosis and treatment with antibiotics. This is a major function of primary care systems. Recent increases in rheumatic fever may herald a return of the problem, perhaps due to inadequate access to primary care in the United States for large sectors of the population, along with crowding and possibly poor access to medical care due to lack of or inadequate health insurance.

Where access to primary care services is limited, infections with streptococci can result in a heavy burden of chronic heart and kidney disease with substantial health, emotional, and financial tolls. Measures to improve access to care and public information are needed to assure rapid and effective care to prevent chronic and costly conditions.

Zoonoses

Zoonoses are infectious diseases transmissible from vertebrate animals to humans. Common examples of zoonoses of public health importance in nonindustrialized countries include brucellosis and rabies. In industrialized countries, salmonellosis, mad cow disease, and influenza have reinforced the importance of relationships of animal and human health. Strong cooperation between public health and veterinary public health authorities are required to monitor and to prevent such diseases. Zoonoses have been described and known over many centuries. They involve all types of agents: bacteria, parasites, viruses, and unconventional agents. Bacterial organisms transmitted by animals include salmonellosis and campylobacteriosis, anthrax, brucellosis, *E. coli*, leptospirosis, plague, shigellosis, and tularemia.

Viruses transmitted by animals include *rabies*, which is a disease of carnivores and bats mainly transmissible to humans by bites. Almost all persons severely exposed to rabid animals will die if not treated. An estimated 55,000 persons, mainly children, die of this disease in the world every year mostly from infected dogs. Control measures focus on immunization of domestic animals and household pets. Infected dog-bite transmission is responsible for most human deaths.

Other viral zoonoses are avian influenza, Crimean-Congo hemorrhagic fever, Ebola, and Rift Valley fever. Bovine spongiform encephalopathy is thought to be the cause of variant Creutzfeldt-Jakob disease (vCJD), which is a neurologic disease different from CJD, leading to death in humans.

Other important zoonoses are brucellosis and echinococcosis/hydatidosis, for example. Zoonoses still represent significant and often neglected public health threats. They are affecting hundreds of thousands of people especially in developing countries, although many are preventable, with essential veterinary public health measures.

Brucellosis

Brucellosis is a disease occurring in cattle (*Brucella abortus*), in dogs (*Br. canis*), in goats and sheep (*Br. melitensis*), and in pigs (*Br. suis*). Humans are affected mainly through ingestion of contaminated milk products, by contact, or inhalation. Brucellosis (also known as relapsing, undulant, Malta, or Mediterranean fever) is a systemic bacterial disease of acute or insidious onset characterized by fever, headache, weakness, sweating, chills, arthralgia, depression, weight loss, and generalized malaise. Spread is by contact with tissues, blood, urine, vaginal discharges, but mainly by ingestion of raw milk and dairy products from infected animals. The disease may last from a few days to a year or more. Complications include osteoarthritis and relapses. Case fatality is under 2 percent, but disability is common and can be pronounced.

The disease is primarily seen in Mediterranean countries, the Middle East, India, central Asia, and Central and South America. Brucellosis occurs primarily as an occupational disease of persons working with and in contact with tissues, blood, and urine of infected animals, especially goats and sheep. It is an occupational hazard

for veterinarians, packing house workers, butchers, tanners, and laboratory workers. It is also transmitted to consumers of unpasteurized milk from infected animals. Animal vectors include wild animals, so that eradication is virtually impossible. Diagnosis is confirmed by laboratory findings of the organism in blood or other tissue samples, or with rising antibody titers in the blood, with confirmation by blood cultures.

Clinical cases are treated with antibiotics. Epidemiologic investigation may help track down contaminated animal flocks. Routine immunization of animals, monitoring of animals in high-risk areas, quarantining sick animals, destroying infected animals, and pasteurizing milk and milk products prevent spread of the disease. Control measures include educating farmers and the public not to use unpasteurized milk. Individuals who work with animals (cattle, swine, goats, sheep, dogs, coyotes) should take special precautions when handling animal carcasses and materials. Testing animals, destroying carriers, and enforcing mandatory pasteurization will restrict the spread of the disease. This is an economic as well as public health problem, requiring full cooperation between ministries of health and of agriculture.

Rabies

Rabies is primarily a disease of animals, with a variety of wild animals serving as a reservoir for this disease, including foxes, wolves, bats, skunks, and raccoons, who may infect domestic animals such as dogs, cats, and farm animals. Animal bites break the skin or mucous membrane, allowing entry of the virus from the infected saliva into the bloodstream. The incubation period of the virus is 2–8 weeks; it can be as long as several years or as short as 5 days, so that postexposure preventive treatment is a public health emergency.

The clinical disease often begins with a feeling of apprehension, headache, pyrexia, followed by muscle spasms, acute encephalitis, and death. Fear of water ("hydrophobia") or fear of swallowing is a characteristic of the disease. Rabies is almost always fatal within a week of onset of symptoms. There is no effective treatment, so control relies on vaccination of animals, rapid prophylaxis of exposed people, and prevention of contact with biting and scratching animals. The disease is estimated to cause 30,000 deaths annually, primarily in developing countries. It is uncommon in developed countries.

Rabies control focuses on prevention in humans, domestic animals, and wildlife. Prevention in humans is based on preexposure prophylaxis for groups at risk (e.g., veterinarians, zoo workers) and post-exposure immune globulin and vaccine administration for persons bitten by potentially rabid animals. Because reducing exposure of pets to wild animals is difficult, immunization of domestic animals is one of the most important preventive measures. Prevention in domestic animals is by mandatory immunization of household pets. All domestic animals should be immunized at age 3 months and revaccinated according to veterinary instructions.

Prevention in wild animals to reduce the reservoir is successful in achieving local eradication in settings where reentry from neighboring settings is limited. Since 1978, the use of oral rabies immunization has been successful in reducing the population of wild animals infected by the rabies virus. Rabies eradication efforts, using aerial distribution of baits containing fox rabies vaccine in affected areas of Belgium, France, Germany, Italy, and Luxembourg, have been under way since 1989. The number of rabies cases in these affected areas has declined by some 70 percent. Switzerland is now virtually rabies-free because of this vaccination program. The potential exists for focal eradication, especially on islands or in partially restricted areas with limited possibilities of wild animal entry. Livestock need not be routinely immunized against rabies, except in high-risk areas. Where bats are major reservoirs of the disease, as in the United States, eradication is not presently feasible.

Salmonella

Salmonella, discussed later in this chapter under diarrheal diseases, is one of the most common infectious diseases among animals and is easily spread to humans via poultry, meat, eggs, and dairy products. Transmission may also occur from contact with infected animals, particularly reptile pets. Specific antigenic types are associated with foodborne transmission to humans, causing generalized illness and gastroenteritis. Severity of the disease varies widely, but the diseases can be devastating among vulnerable population groups, such as young children, the elderly, and the immunocompromised. Epidemiologic investigation of common food source outbreaks may uncover hazardous food handling practices. Laboratory confirmation or serotypes help in monitoring the disease. Prevention is by maintaining high standards of food hygiene in processing, inspection and regulation, food handling practices, and hygiene education.

Anthrax

Bacillus anthracis causes a bacterial infection in herbivore animals. Its spores contaminate soil worldwide. It affects humans exposed in occupational settings. Transmission is cutaneous by contact, gastrointestinal by ingestion, or respiratory by inhalation. It has gained recent attention (Iraq, 1997) as a highly potent agent for germ warfare or terrorism. In 2001, anthrax was used as a bioterror agent against the United States. Twenty-two people were infected, with a 50 percent case mortality rate.

Although most *B. anthracis* strains are susceptible to common antibiotics, concerns over the existence of resistant "weaponized anthrax" has prompted extensive planning to

counter the possibility of repeated attacks. Limited supplies of vaccine are available; however, in the absence of an epidemic, use is only justified for veterinarians, key public health workers, and soldiers or laboratory personnel with higher risk for exposure.

Creutzfeldt-Jakob Disease

Creutzfeldt-Jakob disease is a degenerative disease of the central nervous system linked to consumption of beef from cattle infected with bovine spongiform encephalopathy. It is transmitted by prion proteins in animal feed prepared from contaminated animal material and in transplanted organs. This disease was identified in the United Kingdom linked to infected cattle leading to a 1997 ban on British beef in many parts of the world and slaughter of large numbers of potentially contaminated animals.

Other Major Zoonotic Diseases

The tapeworm causing diphyllobothriasis (*Diphyllobothrium latum*) is widespread in North American freshwater fish, passing from crustacean to fish to humans by eating raw freshwater fish. It is especially common among Inuit peoples and may be asymptomatic or cause severe general and abdominal disorder. Food hygiene (freezing and cooking of meat) is recommended; treatment is by anthelmintics.

Leptospiroses are a group of zoonotic bacterial diseases found worldwide in rats, raccoons, and domestic animals. It affects farmers, sewer workers, dairy and abattoir workers, veterinarians, military personnel, and miners with transmission by exposure to or ingestion of urine-contaminated water or tissues of infected animals. It is often asymptomatic or mild, but may cause generalized illness like influenza, meningitis, or encephalitis. Prevention requires education of the public in self-protection and immunization of workers in hazardous occupations, along with immunization and segregation of domestic animals and control of wild animals.

VECTOR-BORNE DISEASES

Vector-borne diseases are a group of diseases in which the infectious agent is transmitted to humans by crawling or flying insects. The vector is the intermediary between the reservoir and the host. Both the vector and the host may be affected by climatic conditions; mosquitoes thrive in warm, wet weather, and are suppressed by cold weather; humans may wear less protective clothing in warm weather.

Malaria

The only important reservoir of malaria is humans. Its mode of transmission is from person to person via the bite of an infected female *Anopheles* mosquito (Ronald Ross, Nobel Prize, 1902). The causative organism is a single cell parasite with four species: *Plasmodium vivax, P. malariae, P. falciparum,* and *P. ovale*. Clinical symptoms are produced by the parasite invading and destroying red blood cells. The incubation period is approximately 12–30 days, depending on the specific *Plasmodium* involved. Some strains of *P. vivax* may have a protracted incubation period of 8–10 months and even longer for *P. ovale*. The disease can also be transmitted through infected blood transfusions. Confirmation of diagnosis is by demonstrating malaria parasites on blood smears.

Falciparum malaria, the most serious form, presents with fever, chills, sweats, and headache. It may progress to jaundice, bleeding disorders, shock, renal or liver failure, encephalopathy, coma, and death. Prompt treatment is essential. Case fatality rates in untreated children and adults are above 10 percent. An untreated attack may last 18 months. Other forms of malaria may present as a nonspecific fever. Relapse of the *P. ovale* may occur up to 5 years after initial infection; malaria may persist in chronic form for up to 50 years.

Malaria control advanced during the 1940s to 1960s through improved chloroquine treatment and use of DDT for vector control with optimism for eradication of the disease. However, control regressed in many developing countries as allocations for environmental control and case findings/treatment were reduced. There has also been an increase in drug resistance, so that this disease is now an extremely serious public health problem in many parts of the world. The need for a vaccine for malaria control is now more apparent than ever.

WHO estimates sub-Saharan Africa had 270 million new malaria cases, with 5 percent in children up to age 5. Over 1 million deaths occur annually from malaria, more than two-thirds of them in sub-Saharan Africa, and up to 50 percent of health expenditures go to treatment of malaria patients. Large areas, particularly in forest or savannah regions with high rainfall, are holoendemic. In higher altitudes, endemicity is lower, but epidemics do occur. Chloroquine-resistant *P. falciparum* has spread throughout Africa, accompanied by an increasing incidence of severe clinical forms of the disease. The World Bank estimates that 11 percent of all disability-adjusted life years (DALYs) lost per year in sub-Saharan Africa are from malaria, which places a heavy economic burden on the health systems.

In the Americas, the number of cases detected has risen every year since 1974, and the WHO estimates there to have been 2.2–2.5 million cases in 1991. The nine most endemic countries in the Americas achieved a 60 percent reduction in malaria mortality between 1994 and 1997. In 2002, CDC reports that of 1337 malaria cases in the United States, all but 5 were imported, i.e., acquired in malaria-endemic countries.

Malaria kills over 1 million people annually and infects between 350 and 500 million (WHO, 2008). Sub-Saharan Africa is the hardest hit region with 90 percent of these deaths, especially among children, and it has a serious impact on health and economic development. There is an increase in resistant strains to the major available drugs and of the mosquitoes to insecticides in use.

Vector control, case finding, and treatment remain the mainstay of control. Use of insecticide-impregnated bed nets and curtains, residual house spraying, and strengthened vector control activities are important, as are early diagnosis and carefully monitored treatment with monitoring for resistance. Control of malaria will ultimately depend on a safe, effective, and inexpensive vaccine. Attempts to develop a malaria vaccine have been unsuccessful to date due to the large number of genetic types of *P. falciparum* even in localized areas. Twenty-three prospective *P. falciparum* vaccines are currently in clinical trials, with some reported effectiveness. Research in vaccines for malaria has also been hampered by the fact that it is a relatively low priority for vaccine manufacturers because of the minimal potential for financial benefit. Because of increasing drug resistance, research on malaria has concentrated on the pharmacologic aspects of the disease. Effective control of malaria will require both new drugs for resistant infections, and primary prevention through vector control, with hopes for eventual vaccine development.

In 1998, WHO initiated a campaign to "Roll Back Malaria" and maintain the dream of eradication in the future; Malaria is included in MDG6 and Rollback Malaria for the period 2006–2015. Effective low-technology interventions include community-based case finding, early treatment with good quality insecticides, and vector control. The use of community health workers and widespread provison of insecticide-impregnated bed nets in endemic areas has shown promising results. Local control and even eradication can be achieved with currently available technology. This requires an integration of public health and clinical approaches with strong political commitment internationally and nationally in the affected countries.

Rickettsial Infections

The Rickettsieae are obligate parasites; they can only replicate in living cells, but otherwise they have characteristics of bacteria. This is a group of clinically similar diseases, usually characterized by severe headache, fever, myalgia, rash, and capillary bleeding causing damage to brain, lungs, kidneys, and heart. Identification is by serological testing for antibodies, but the organisms can also be cultured in laboratory animals, embryonic eggs, or in cell cultures. The organisms are transmitted by arthropod vectors such as lice, fleas, ticks, and mites. The diseases caused millions of deaths during war and famine periods prior to the advent of antibiotics.

These diseases appear in nature in ways that make them impossible to eradicate, but clinical diagnosis, host protection, and vector control can help reduce the burden of disease and deal with outbreaks that may occur. Public education regarding self-protection, appropriate clothing, tick removal, and localized control measures such as spraying and habitat modification are useful.

Epidemic typhus, first identified in 1836, is due to *Rickettsia prowazekii*. Spread primarily by the body louse, typhus was the cause of an estimated 3 million deaths, especially during war and famine, in Poland and the Soviet Union from 1915–1922. Untreated, the fatality rate is 5–40 percent. Typhus responds well to antibiotics. It is currently largely confined to endemic foci in central Africa, central Asia, eastern Europe, and South America. It is preventable by hygiene and pediculicides such as DDT and lindane. A vaccine is available for exposed laboratory personnel.

Murine typhus is a mild form of typhus due to *Rickettsia typhi*, which is found worldwide and spread in rodent reservoirs. Scrub typhus, also known as Tsutsugamushi or Japanese river fever, is located throughout the Far East and the Pacific islands, and was a serious health problem for U.S. armed forces in the Pacific during World War II. It is spread by the *Rickettsia tsutsugamushi* and has a wide variation in case fatality according to region, organism, and age of patient.

Rocky Mountain spotted fever is a well-known and deadly form of tick-borne typhus due to *Rickettsia rickettsii*, occurring in western North America, Europe, and Asia. Q fever is a tick-borne disease caused by *Coxiella burnetii* and is worldwide in distribution, usually associated with farm workers, in both acute and chronic forms. Regular antitick spraying of sheep, cows, and goats helps protect exposed workers. Protective clothing and regular removal of body ticks help protect exposed persons.

Arboviruses (Arthropod-Borne Viral Diseases)

Arthropod-borne viral diseases are caused by a diverse group of viruses which are transmitted between vertebrate animals (often farm animals or small rodents) and people by the bite of blood-feeding vectors such as mosquitoes, ticks, and sandflies and by direct contact with infected animal carcasses. Usually the viruses have the capacity to multiply in the salivary glands of the vector, but some are carried mechanically in their mouth parts.

These viruses cause acute central nervous system infections (meningoencephalitis), myocarditis, or undifferentiated viral illnesses with polyarthritis and rashes, or severe hemorrhagic febrile illnesses. Arbovirus diseases

are often asymptomatic in vertebrates but may be severe in humans. Over 250 antigenetically distinct arboviruses are associated with disease in humans, varying from benign fevers of short duration to severe hemorrhagic fevers. Each has a specific geographic location and vector and specific clinical and virologic characteristics, but they can spread globally via travelers and become endemic in new regions. They are of international public health importance because of the potential for spread via natural phenomena and modern rapid transportation of vectors and persons incubating the disease or ill with it, with potential for further spreading at the point of destination.

Encephalitides

Arboviruses are responsible for a large number of encephalitic diseases characterized by mode of transmission and geographic area. Mosquito-borne arboviruses causing encephalitis include Eastern and Western Equine, Venezuelan, Japanese, and Murray Hill encephalitides. Japanese encephalitis is caused by a mosquito-borne arbovirus found in Asia and is associated with rice-growing areas. It is characterized by headache, fever, convulsions, and paralysis, with fatality rates in severe cases as high as 60 percent. A currently available vaccine is used routinely in endemic areas (Japan, Korea, Thailand, India, and Taiwan) and for persons traveling to infected areas. Tick-borne arboviruses causing encephalitis include the Powassan virus, which occurs sporadically in the United States and Canada. Tick-borne encephalitis is endemic in eastern Europe, Scandinavia, and the former Soviet Union.

West Nile Virus (WNV)

This virus identified first in Africa in 1937, with wide distribution in Europe, southern USSR, the Middle East, Africa, and South Asia, appearing in Egypt and Israel in the 1950s, has now become worldwide in scope. An epidemic of mosquito-borne encephalitis in New York City in 1999 included 54 cases and 6 deaths due to the West Nile Fever virus, never before found in the United States. The virus has since spread throughout North America, with animal and human cases in nearly every state of the United States. Use of strategically located sentinel chicken flocks has been very effective in determining the geographical distribution of WNV and predicting local risks for infection. When birds test positive in a new area, health care providers are alerted to the signs and symptoms of WNV, increasing the effectiveness of surveillance, early intervention, and prevention. This highly successful model may potentially be applied to other zoonotic diseases. While only 20 percent of infected individuals develop clinical disease, the consequences of infection can be severe, especially in elderly and immunocompromised people. Treatments for WNV are supportive and there is no vaccine available. The only effective means of prevention are vector control programs and personal protection against mosquito bites.

In the United States, the CDC reports that during 2006, WNV transmission to humans or animals recurred and expanded into many countries that had not previously reported transmission. Cases of WNV neuroinvasive disease (WNND) increased from 2003–2006. Extrapolations from past serosurveys suggested an estimated 41,750 cases of non-neuroinvasive WNV disease occurred in 2006 as compared to the 2770 reported cases. The spread of WNF indicated need for continuing surveillance, mosquito control, promotion of personal protection from mosquito bites, and research into additional prevention strategies.

Chikungunya

Chikungunya fever is a viral disease spread by the bite of infected mosquitoes. It was mainly located in India and Southeast Asia, causing a severe denguelike illness that is mostly nonfatal. The disease has spread to Europe with outbreaks in France and later Italy following importation from India by a single traveler. Because it was a large outbreak (over 197 cases) in 2007, concerns were raised that it might become endemic.

Rift Valley Fever

Rift Valley fever (RVF) is a virus spread by mosquitoes and other insect vectors. It affects animals and humans who are in direct contact with the meat or blood of affected animals. The virus causes a generalized illness in humans with encephalitis, hemorrhages, retinitis and retinal hemorrhage leading to partial or total blindness, and death (1–2 percent). It also causes universal abortion in ewes and a high percentage of death in lambs.

The normal habitat is in the Rift Valley of eastern Africa (the Great Syrian–African Rift), often spreading to southern Africa, depending on climactic conditions. The primary reservoir and vector is the *Aedes* mosquito, and affected animals serve to multiply the virus which is transmitted by other vectors and direct contact with animal fluids to humans.

An unusual spread of RVF northward to the Sudan and along the Aswan Dam reservoir to Egypt in 1977–1978 caused hundreds of thousands of animal deaths, with 18,000 human cases and 598 deaths. RVF appeared again in Egypt in 1993. This disease is suspected to be one of the ten plagues of Egypt leading to the exodus of the Children of Israel from Egypt during pharaonic-biblical times.

In 1997, an outbreak of RVF in Kenya, initially thought to be anthrax, with hundreds of cases and dozens of deaths, was related to abnormal rainy season and vector conditions. Satellite monitoring of rainfall and vegetation is being used to predict epidemics in Kenya and surrounding countries. Animal immunization, monitoring, vector

control, and reduced contact with infected animals can limit the spread of this disease.

RVF has reappeared in the Middle East in Yemen and Saudi Arabia since 2000 and may have become endemic in the region.

Hemorrhagic Fevers

Arboviruses can also cause hemorrhagic fevers. These are acute febrile illnesses, with extensive hemorrhagic phenomena (internal and external), liver damage, shock, and often high mortality rates. The potential for international transmission is high.

Yellow Fever

Yellow fever is an acute viral disease of short duration and varying severity with jaundice. It can progress to liver disease and severe intestinal bleeding. The case fatality rate is 5 percent in endemic areas, but may be as high as 50 percent in nonendemic areas and in epidemics. It caused major epidemics in the Americas in the past, but was controlled by elimination of the vector, *Aedes aegypti*. A live attenuated vaccine is used in routine immunization endemic areas and recommended for travelers to infected areas. Determining the mode of transmission and vector control of yellow fever played a major role in the development of public health (see Chapter 1). In 1997, the WHO reported 200,000 cases and 30,000 deaths from yellow fever globally. Originally imported to the Americas from Africa, yellow fever is endemic in 10 countries in Central and South America, and is now spreading as well as in Asia.

Dengue Hemorrhagic Fever

Dengue hemorrhagic fever is an acute sudden-onset viral disease, with 3–5 days of fever, intense headache, myalgia, arthralgia, gastrointestinal disturbance, and rash. Hemorrhagic phenomena can cause case fatality rates of up to 50 percent. Epidemics can be explosive, but adequate treatment can greatly reduce the number of deaths. Dengue occurs in southeast Asia, the Pacific Islands, Australia, West Africa, the Caribbean, and Central and South America. An epidemic in Cuba in 1981 included more than 500,000 cases, and 158 deaths. Vector control of the *A. aegypti* mosquito resulted in control of the disease during the 1950s–1970s, but reinfestation of mosquitoes led to increased transmission and epidemics in the Pacific Islands, Caribbean, and Central and South America in the 1980s and 1990s (Box 4.12).

Outbreaks in Vietnam included 370,000 cases in 1987, another 116,000 cases in 1990, and a similar-sized outbreak in 1997. Indonesia had over 13,000 cases in 1997 with 240 deaths, and in 1998 over 19,000 cases (January–May) with at least 531 deaths. In 1998, epidemics of dengue were reported in Fiji, the Cook Islands, New Caledonia, and northern Australia. Monkeys are the main reservoir, and the vector is the *A. aegypti* mosquito. No vaccine is currently available, and management is by vector control.

Box 4.12 Dengue and Dengue Haemorrhagic Fever

Dengue fever, a severe influenza-like illness, and dengue hemorrhagic fever are closely related conditions caused by four distinct viruses transmitted by *Aedes aegypti* mosquitoes. Dengue is the world's most important mosquito-borne virus disease. A total of 2,500 million people worldwide are at risk of infection. An estimated 20 million cases occur each year, of whom 500,000 need to be hospitalized. This is a spreading problem, especially in cities in tropical and subtropical areas. Major outbreaks were reported in Colombia, Cuba, and many other locations in 1997.

"The geographical spread of both the mosquito vectors and the viruses has led to the global resurgence of epidemic dengue fever and emergence of dengue hemorrhagic fever (dengue/DHF) in the past 25 years with the development of hyperendemicity in many urban centers of the tropics.

"Recovery from infection by one provides lifelong immunity against that serotype but confers only partial and transient protection against subsequent infection by the other three. There is good evidence that sequential infection increases the risk of more serious disease resulting in DHF.

"DHF was first recognized in the 1950s during the dengue epidemics in the Philippines and Thailand. By 1970, nine countries had experienced epidemic DHF and now, the number has increased more than fourfold and continues to rise. Today emerging DHF cases are causing increased dengue epidemics in the Americas, and in Asia, where all four dengue viruses are endemic. DHF has become a leading cause of hospitalization and death among children in several countries."

Currently vector control is the available method for dengue and DHF prevention and control but research on dengue vaccines for public health use is in process.

Sources: World Health Organization. 1998. *World Health Report* 1998. Geneva: World Health Organization.
WHO and Dengue at WHO Geneva, http://www.who.int/esr/disease/dengue/en/ [accessed October 30, 2007].

Other Hemorrhagic Fevers

Lassa Fever

Lassa fever was first isolated in Lassa, Nigeria, in 1969 and is widely distributed in west Africa, with 200,000–400,000 cases and 5000 deaths annually. It is spread by direct contact with blood, urine, or secretions of infected rodents and by direct person-to-person contact in hospital settings. The disease is characterized by a persistent or spiking fever for 2–4 weeks, and may include severe hypotension, shock, and hemorrhaging. The case fatality rate is 15 percent.

Marburg Disease

Marburg disease is a viral disease with sudden onset of generalized illness, malaise, fever, myalgia, headache, diarrhea, vomiting, rash, and hemorrhages. It was first seen in Marburg, Germany, in 1967, following exposure to green monkeys. Person-to-person spread occurs via blood, secretions, organs, and semen. Case fatality rates can be over 50 percent.

Ebola Fever

Ebola fever is a viral disease with sudden onset of generalized illness, malaise, fever, myalgia, headache, diarrhea, vomiting, rash, and hemorrhages. It was first found in Zaire and Sudan in 1976 in outbreaks which killed more than 400 persons. It is spread from person to person by the blood, vomitus, urine, stools, and other secretions of sick patients, with a short incubation period. The disease has case fatality rates of up to 90 percent. An outbreak of Ebola among laboratory monkeys in a medical laboratory near Washington, DC, was contained with no human cases. The reservoir for the virus is thought to be rodents.

An outbreak of Ebola in May 1995 in the town of Kikwit, Zaire, killed 245 persons out of 316 cases (78 percent case fatality rate). This outbreak caused international concern that the disease could spread, but it remained localized. Another outbreak of Ebola virus occurred in Gabon in early 1996, with 37 cases, 21 of whom had direct exposure to an infected monkey, the remainder by human-to-human contact, or not established; 21 of the cases died (57 percent). Frequent similar epidemics have continued. This disease is considered highly dangerous unless outbreaks are effectively controlled. Once identified, an Ebola epidemic becomes an international emergency; public health workers from across the world are involved in control and intervention through WHO- and CDC-directed projects. In Zaire, lack of basic sanitary supplies, such as surgical gloves for hospitals, almost ensures that this disease will spread when it recurs.

Lyme Disease

Lyme disease is characterized by the presence of a rash, musculoskeletal, neurologic, and cardiovascular symptoms. Confirmation is by laboratory investigation. It is the most common vector-borne disease in the United States, with 64,000 cases reported between 2003 and 2005. It primarily affects children in the 5–14 age group and adults aged 30–49. Lyme disease is preventable by avoiding contact with ticks, by applying insect repellant, wearing long pants and long sleeves in infected areas, and by the early removal of attached ticks. Several U.S. manufacturers have developed vaccines; however, implementation of programs has been difficult due to difficulties in adverse event reporting and tracking (Box 4.13).

Box 4.13 Lyme Disease

In the mid 1970s, a mother of two young boys who were recently diagnosed with arthritis in the town of Lyme, Connecticut, conducted a private investigation among other town residents. She mapped each of the six arthritis cases in the town, cases which had occurred in a short time span among boys living in close proximity. This suggested that this syndrome of "juvenile rheumatoid arthritis" was perhaps connected with the boys playing in the woods. She presented her data to the head of rheumatology at Yale Medical School in New Haven, who investigated this "cluster of a new disease entity." Some parents reported that their sons had experienced tick bites and a rash before onset of the arthritis. A tick-borne, spiral-shaped bacterium, a spirochete, *Borrelia burgdorferi*, was identified as the organism, and *Ixodes* ticks were shown to be the vector. Cases respond well to antibiotic therapy.

Lyme disease infects approximately 20,000 people per year. Risk is highest in the northeast, north central, and mid-Atlantic regions. The disease accounts for over 90% of vector-borne disease in the United States and was the ninth leading reported infection in 1995. Lyme disease has been identified in many parts of North America, Europe, the former Soviet Union, China, and Japan. Personal hygiene for protection from ticks and environmental modification are important to limit spread of the disease.

Sources: Centers for Disease Control. 2007. *MMWR*,. 56:573–576.
Centers for Disease Control. 1996. *MMWR*, 45 481–484
Centers for Disease Control. 1997. *MMWR*, 46:23.
Lyme disease website, available at http://www.cdc.gov/ncidad/disease/lyme/lyme.htm

PARASITIC DISEASES

Medically important parasites are animals that live, take nourishment, and thrive in the body of a host, which may or may not harm the host, but never bring benefit. They include unicellular organisms such as protozoa (malaria, *Giardia*, amebiasis, and *Cryptosporidium*), and helminths (worms), which are categorized as nematodes, cestodes, and trematodes (Box 4.14).

Public health continues to face the problems of parasitic diseases in the developing world. Increasingly, parasitic diseases are being recognized in industrialized countries. Giardiasis and *Cryptosporidium* infections in waterborne and other outbreaks have occurred in the United States. Parasitic diseases such as malaria are among the most common causes of illness and death in the world. Milder illnesses such as giardiasis and trichomoniasis cause widespread morbidity. Intestinal infestations with worms may cause severe complications, although they commonly cause chronic low-grade symptomatology and iron-deficiency anemia. Deworming every six months has become an effective part of the Expanded Programme of Immunization (EPI plus) along with Vitamin A supplementation and insecticide impregnated bed nets for children.

Echinococcosis

Echinococcosis (hydatid cyst disease) is infection with *Echinococcus granulosus*, a small tapeworm commonly found in dogs. The tapeworm forms unilocular (single, noncompartmental) cysts in the host, primarily in the liver and lungs, but they can also grow in the kidney, spleen, central nervous system, or in bones. Cysts, which may grow up to 10 cm in size, may be asymptomatic or, if untreated, may cause severe symptoms and even death. This parasite is common where dogs are used with herd grazing animals and also have intimate contact with humans.

The Middle East, Greece, Sardinia, north Africa, and South America are endemic areas, as are a few areas in

Box 4.14 Neglected Tropical Diseases

"At least 1 billion people suffer from one or more neglected tropical diseases (NTDs), such as Buruli ulcer, cholera, cysticercosis, dracunculiasis (guinea-worm disease), food-borne trematode infections (such as fascioliasis), hydatidosis, leishmaniasis, lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis, trachoma and trypanosomiasis, although there are other estimates that suggest the number could be much higher. Several of these diseases, and others such as dengue, are vector-borne. Often, those populations most affected are also the poorest and most vulnerable and are found mainly in tropical and subtropical areas of the world. Some diseases affect individuals throughout their lives, causing a high degree of morbidity and social stigmatization and abuse.

"For a large group of these diseases — mainly helminthic infections — effective, inexpensive or donated drugs are available for their prevention and control. These tools, when used on a large scale, are able to wipe out the burden caused by these ancient scourges of humanity. For leprosy, treatment with effective antibiotics is leading to the elimination of this ancient disabling disease. There is also a cost-effective approach to treating yaws that could lead to elimination and final eradication of this debilitating disease that may cause gross deformation. In the case of blinding trachoma, the use of the recommended strategy (SAFE) of an effective antibiotic is enhancing the progress toward final elimination. Large-scale, regular treatment plays a central role in the control of many NTDs such as filariasis, onchocerciasis, schistosomiasis, and soil-transmitted nematode infections. For example, regular chemotherapy against intestinal worms reduces mortality and morbidity in preschool children, improves the nutritional status and academic performance of schoolchildren, and improves the health and well-being of pregnant women and their babies.

"There is a second group of NTDs for which the only clinical option currently available is systematic case-finding and management at an early stage. These diseases include Buruli ulcer, Chagas' disease, cholera and other diarrheal diseases, human African trypanosomiasis, and leishmaniasis. Simple diagnostic tools and safe and effective treatment regimens need to be developed urgently for some of these diseases. However, even for these infections, systematic use of the present, imperfect tools at an early stage can dramatically reduce mortality and morbidity. For others, vector control tools are available and present the main method of transmission control, as in the case of Chagas' disease.

There are examples of great successes in the fight against both of these groups of NTDs. Since 1985, 14.5 million patients have been cured of leprosy through multi-drug therapy; today, less than a million people are affected by the disease. Before the start of the Guinea-worm Eradication Programme in the early 1980s, an estimated 3.5 million people in 20 endemic countries were infected with the disease. In 2005, only about 10,000 cases were reported in 9 endemic countries, and the programme is moving towards eradication. Onchocerciasis has freed more than 25 million hectares of previously onchocerciasis-infected land available for resettlement and agricultural cultivation, thereby considerably improving development prospects in Africa and Latin America.

Increased awareness and advocacy are needed to draw attention to the realistic prospect of reducing the negative impact of NTDs on the health and social and economic well-being of affected communities."

Source: World Health Organization. http://www.who.int/neglected_diseases/en/ [accessed October 10, 2007]

the United States and Canada. The human disease has been eliminated in Cyprus and Australia. While the dog is the major host, intermediate hosts include sheep, cattle, pigs, horses, moose, and wolves. Preventive measures include education in food and animal contact hygiene, destroying wild and stray dogs, and keeping dogs from the viscera of slaughtered animals.

A similar, but multilocular, cystic hydatid disease is widely found in wild animal hosts in areas of the northern hemisphere, including central Europe, the former Soviet Union, Japan, Alaska, Canada, and the north-central United States.

Another echinococcal disease (*Echinococcus vogeli*) is found in South America, where its natural host is the bush dog and its intermediate host is the rat. The domestic dog also serves as a source of human infection.

Surgical resection is not always successful, and long-term medical treatment may be required. Control is through awareness and hygiene as well as the control of wild animals that come in contact with humans and domestic animals. Control may require cooperation between neighboring countries.

Tapeworm

Tapeworm infestation (taeniasis) is common in tropical countries where hygienic standards are low. Beef (*Taenia saginata*) and pork (*T. solium*) tapeworms are common where animals are fed with water or food exposed to human feces. *T. solium* is especially deadly; delay in diagnosis and treatment may lead to severe disease, including neurologic cysticercosis. In developing countries, infection is associated with pork consumption, while in the United States, several epidemics have occurred from eating carnivorous game animals such as mountain lions and bears. Freezing or cooking meat, especially that of pigs and carnivorous mammals, is essential to destroy the tapeworm. Fish tapeworm (*Diphyllobothrium latum*) is common in populations living primarily on uncooked fish, such as Inuit, Eastern European, and Scandinavian. These tapeworms are usually associated with northern climates.

Toddlers are especially susceptible to dog tapeworm (*Dipylidium caninum*), which is present worldwide, and domestic pets are often the source of oral–fecal transmission of the eggs. The disease is usually asymptomatic. Similarly, dwarf tapeworm (*Hymenolepis nana*) is transmitted through oral–fecal contamination from person to person, or via contaminated food or water. Rat tapeworm (*Hymenolepis diminuta*) also mostly affects young children.

Onchocerciasis

Onchocerciasis (river blindness) is a disease caused by a parasitic worm, which produces millions of larvae that move through the body causing intense itching, debilitation, and eventually blindness. The disease is spread by a blackfly that transmits the larva from infected to uninfected people. It is primarily located in sub-Saharan Africa and in Latin America, with over 120 million persons at risk. Control is by a combination of activities including environmental control by larvicidal sprays to reduce the vector population, protection of potential hosts by protective clothing and insect repellents, and case treatment.

A WHO-initiated program for onchocerciasis control started in 1974 is sponsored by four international agencies: the Food and Agriculture Organization (FAO), the United Nations Development Program (UNDP), the World Bank, and WHO. It covers 11 countries in sub-Saharan Africa, focusing on control of the blackfly by destroying its larvae, mainly via insecticides sprayed from the air. The Vision 2020 program of the WHO aims for control of river blindness by the year 2020.

The program has been successful in protecting some 30 million persons and helping 1.5 million infected persons to recover from this disease. WHO estimates that the program prevented 500,000 cases of blindness by 2000 and has freed 25 million hectares of land for resettlement and cultivation. The program cost $570 million. This investment is considered by the World Bank to have a return of 16–28 percent in terms of large-scale land reuse and improved output of the population. A WHO program, the African Program for Onchocerciasis Control (APOC), started in 1996, includes Ivermectin and selective vector control efforts by spraying for the blackfly. This involves 30 countries in Africa, and 6 in a similar program in South America (see http://www/who.int/ocp).

Dracunculiasis

Dracunculiasis (Guinea worm disease) is a parasitic disease of great public health importance in India, Pakistan, and central and west Africa. It is an infection of the subcutaneous and deeper tissues caused by a large (60 cm) nematode, usually affecting the lower extremities and causing pain and disability. The nematode causes a burning blister on the skin when it is ready to release its eggs. After the blister ruptures, the worm discharges larvae whenever the extremity is in water. The eggs are ingested in contaminated water and the larvae released migrate through the viscera to locate as adults in the subcutaneous tissue of the leg. Incubation is about 12 months. Larvae released in water are ingested by minute crustaceans and remain infective for as long as a month.

Prevention is based on improving the safety of water supplies and by preventing contamination by infected persons. Education of persons in endemic areas to stay out of water sources and to filter drinking water reduces transmission. Insecticides remove the crustaceans. Chlorine

also kills the larvae and the crustaceans which prologue larval infectivity. There is no vaccine. Treatment is helpful, but not definitive.

Dracunculiasis was traditionally endemic in a belt from west Africa through the Middle East to India and central Asia. It was successfully eliminated from central Asia and Iran and has disappeared from the Middle East and from some African countries (Gambia and Guinea).

WHO has promoted the eradication of dracunculiasis. Major progress has been made in this direction. Worldwide prevalence is reported to have been reduced from 12 million cases in 1980 to 3 million in 1990, 152,814 in 1996, and 77,863 cases in 1997. Eradication was anticipated for 2000; however, the Guinea worm remains endemic in several developing African nations. India's reported cases fell from 17,000 in 1987 to 900 in 1992, and the country was free from transmission in 1997. In 1997, formerly high-prevalence countries such as Kenya reported no cases in 1997, while Chad, Senegal, Cameroon, Yemen, and the Central African Republic reported fewer than 30 cases each.

The WHO eradication program was developed successfully as an independent program with its own direction and field staff, but further progress will require the integration of this program with other basic primary care programs in order to be self-sustaining as an integral part of community health. Community-based surveillance systems for this disease are being converted to work for monitoring of other health conditions in the community.

Schistosomiasis

Schistosomiasis is a parasitic infection caused by the trematode (blood fluke) and transmitted from person to person via an intermediate host, the snail. It is endemic in 74 countries in Africa, South America, the Caribbean, and Asia. There are an estimated 200 million persons infected worldwide and more than 600 million at risk for the disease. The clinical symptoms include fever, nausea, vomiting, abdominal pain, diarrhea, and hematuria. The organisms *Schistosoma mansoni* and *S. japonicum* cause intestinal and hepatic symptoms, including diarrhea and abdominal pain. *Schistosoma haematobium* affects the genitourinary tract, causing chronic cystitis, pyelonephritis, with high risk for bladder cancer, the ninth most common cause of cancer deaths globally. A recently identified species, *S. intercalatum,* is genetically unique, but thought to cause both intestinal and genitourinary disease. *S. intercalatum* is largely identified in inhabitants and immigrants from western Africa. Infection by all schistosomes is acquired by skin contact with fresh water containing contaminated snails. The cercariae of the organism penetrate the skin, and in the human host it matures into an adult worm that mates and produces eggs. The eggs are disseminated to other parts of the body from the worm's location in the veins surrounding the bladder or the intestines, and may result in neurologic symptoms.

Eggs may be detected under microscopic examination of urine and stools. Sensitive serologic tests are also available. Treatment is effective against all three major species of schistosomiasis. Eradication of the disease can be achieved with the use of irrigation canals, prevention of contamination of water sources by urine and feces of infected persons, treatment of infected persons, destruction of snails, and health education in affected areas. Persons exposed to freshwater lakes, streams, and rivers in endemic areas should be warned of the danger of infection. Mass chemotherapy in communities at risk and improved water and sanitation facilities are resulting in improved control of this disease.

Leishmaniasis

Leishmaniasis causes both cutaneous and visceral disease. The cutaneous form is a chronic ulcer of the skin, called by various names (e.g., rose of Jericho, oriental sore, and Aleppo boil). It is caused by *Leishmania tropica, L. braziliensis, L. mexicana,* or the *L. donovani* complex. This chronic ulcer may last from weeks to more than a year. Diagnosis is by biopsy, culture, and serologic tests. The organism multiplies in the gut of sandflies (*Phlebotomus* and *Lutzomi*) and is transmitted to humans, dogs, and rodents through bites. The parasites may remain in the untreated lesion for 5–24 months, and the lesion does not heal until the parasites are eliminated.

Prevention is through limiting exposure to the phlebotomines and reducing the sandfly population by environmental control measures. Insecticide use near breeding places and homes has been successful in destroying the vector sandflies in their breeding places. Case detection and treatment reduce the incidence of new cases. There is no vaccine, and treatment is with specific antimonials and antibiotics.

Visceral leishmaniasis (kala azar) is a chronic systemic disease in which the parasite multiplies in the cells of the host's visceral organs. The disease is characterized by fever, the enlargement of the liver and spleen, lymphadenopathy, anemia, leukopenia, and progressive weakness and emaciation. Diagnosis is by culture of the organism from biopsy or aspirated material, or by demonstration of intracellular (Leishman–Donovan) bodies in stained smears from bone marrow, spleen, liver, or blood.

Kala azar is a rural disease occurring in the Indian subcontinent, China, the southern republics of the former U.S.S.R., the Middle East, Latin America, and sub-Saharan Africa. It usually occurs as scattered cases among infants, children, and adolescents. Transmission is by the bite of the infected sandfly with an incubation period of 2–4 months.

There is no vaccine, but specific treatment is effective and environmental control measures reduce the disease prevalence. This includes the use of antimalarial insecticides. In localities where the dog population has been reduced, the disease is less prevalent.

Trypanosomiasis

African Trypanosomiasis (Sleeping Sickness)

Sleeping sickness is a fatal degenerative neurologic disease caused by *Trypanosoma brucei*, transmitted by the tsetse fly, primarily in the African savannahs, affecting cattle and humans. Subspecies are known to cause both acute and chronic forms of sleeping sickness. Some 55 million persons are at risk in sub-Saharan Africa. Between 1998 and 2004, renewed surveillance and control reduced the incidence of African trypanosomiasis from 38,000 to approximately 18,000. Prevention depends on vector control, and effective treatment of human cases.

Chagas' Disease (American Trypanosomiasis)

Chagas' disease is a chronic vector- and blood transfusion–borne parasitic disease (*Trypanosoma cruzi*) which causes significant disability and death. It affects some 17 million persons mainly in Central and South America, with some 300,000 new cases and 45,000 deaths occurring annually. About 30 percent of affected persons develop severe heart disease. While vaccine development is not likely due to the ability of trypanosome antigens to cause autoimmunity and rapid immunologic drift of the organism, two drugs have been developed which show effectiveness in limiting early chronic disease. Brazil achieved elimination of transmission in 1998, after Uruguay (1996) and Venezuela (1997), and followed by Argentina (1999). While the initial WHO elimination goal by 2010 now seems unfeasible, efforts continue to dramatically reduce the incidence of *T. cruzi* infection.

Control is difficult, but control measures include reducing the animal host and vector insect population in its habitat by ecological and insecticide measures, education of the population in prevention by clothing, bed nets, and repellents, and with chemotherapy for case management.

Other Parasitic Diseases

Amebiasis

Amebiasis is an infection with a protozoan parasite (*Entamoeba histolytica*) which exists as an infective cyst. Infestation may be asymptomatic or cause acute, severe diarrhea with blood and mucus, alternating with constipation. *E. histolytica* infection sometimes results in invasive abdominal infestation, severe liver disease, and death.

Amebic colitis can be confused with ulcerative colitis. Diagnosis is by microscopic examination of fresh fecal specimens showing trophozoites or cysts. Transmission is generally via ingestion of fecal-contaminated food or water containing cysts, or by oral–anal sexual practices. Amebiasis is found worldwide. Sand filtration of community water supplies removes nearly all cysts. Suspect water should be boiled. Education regarding hygienic practices with safe food and water handling and disposal of human feces is the basis for control.

Ascariasis

Ascariasis is infestation of the small intestine with the roundworm *Ascaris lumbricoides*, which may appear in the stool, occasionally the nose or mouth, or may be coughed up from lung infestation. The roundworm is very common in tropical countries, where infestation may reach or exceed 50 percent of the population. Children aged 3–8 years are especially susceptible. Infestation can cause pulmonary symptoms and frequently contributes to malnutrition, especially iron-deficiency anemia. Transmission is by ingestion of infective eggs, common among children playing in contaminated areas, or via the ingestion of uncooked products of infected soil. Eggs may remain viable in the soil for years. Vermox and other treatments are effective. Prevention is through education, adequate sanitary facilities for excretion, and improved hygienic practices, especially with food. Use of human feces for fertilizer, even after partial treatment, may spread the infestation. Mass treatment is indicated in high prevalence communities.

Pinworm Disease (Enterobiasis)

Pinworm disease (oxyuriasis) is common worldwide in all socioeconomic classes; however, it is more widespread when crowded and unsanitary living conditions exist. The *Enterobius vermicularis* infestation of the intestine may be asymptomatic or may cause severe perianal itching or vulvovaginitis. It primarily affects schoolchildren and preschoolers. More severe complications may occur. Adult worms may be seen visually or identified by microscopic examination of stool specimens or perianal swabs. Transmission is by the oral–fecal ingestion of eggs. The larvae grow in the small intestine and upper colon. Prevention is by educating the public regarding hygiene and adequate sanitary facilities, as well as by treating cases and investigating contacts. Treatment is the same as for ascariasis. Mass treatment is indicated in high prevalence communities.

Ectoparasites

Ectoparasites include scabies (*Sarcoptes scabiei*), the common bed bug (*Cimex lectularius*), fleas, and lice, including the body louse (*Pediculus humanis*), pubic louse

(*Phthirius pubis*), and the head louse (*Pediculus humanus capitis*). Their severity ranges from nuisance value to serious public health hazard. Head lice are common in schoolchildren worldwide and are mainly a distressing nuisance. The body louse serves as a vector for epidemic typhus, trench fever, and louse-borne relapsing fever. In disaster situations, disinfection and hygienic practices may be essential to prevent epidemic typhus. The flea plays an important role in the spread of the plague by transmitting the organism from the rat to humans. Control of rats has reduced the flea population, but during war and disasters, rat and flea populations may thrive. Scabies, which is caused by a mite, is common worldwide and is transmitted from person to person. The mite burrows under the skin and causes intense itching. All of these ectoparasites are preventable by proper hygiene and the treatment of cases. The spread of these diseases is rapid and therefore warrants attention in school health and public health policy.

LEGIONNAIRE'S DISEASE

Legionnaire's disease (Legionnellosis) is an acute bacterial disease caused by *Legionnelae*, a gram-negative group of bacilli, with 35 species and many serological groups. The first documented case was reported in the United States in 1947, and the first disease outbreak was reported in the United States in 1976 among participants of a veteran's convention in Philadelphia. General malaise, anorexia, myalgia, and headache are followed by fever, cough, abdominal pain, and diarrhea. Pneumonia followed by respiratory failure may follow. The case fatality rate can be as high as 40 percent of hospitalized cases. A milder, nonpneumonic form of the disease (Pontiac fever) is associated with virtually no mortality.

The organism is found in water reservoirs and is transmitted through heating, cooling, and air conditioning systems, as well as from tap water, showers, saunas, and jacuzzi baths. The disease has been reported worldwide. Significant epidemics have occurred on cruise ships, where insufficient air conditioning sanitation and an older, more susceptible clientele are a dangerous combination. Prevention requires the cleaning of water towers and cooling systems, including whirlpool spas. Hyperchlorination of water systems and the replacement of filters is required where cases and/or organisms have been identified. Antibiotic treatment with erythromycin is effective.

LEPROSY

Leprosy (Hansen's disease) was widely prevalent in Europe and Mediterranean countries for many centuries, with some 19,000 leprosaria in the year 1300. Leprosy was largely wiped out during the Black Death in the fourteenth century, but continued in endemic form until the twentieth century. Leprosy is a chronic bacterial infection of the skin, peripheral nerves, and upper airway. In the lepromatous form, there is diffuse infiltration of the skin nodules and macules, usually bilateral and extensive. The tuberculoid form of the disease is characterized by clearly demarcated skin lesions with peripheral nerve involvement. Diagnosis is based on clinical examination of the skin and signs of peripheral nerve damage, skin scrapings, and skin biopsy.

Transmission of the *Mycobacterium leprae* organism is by close contact from person to person, with incubation periods of between 9 months and 20 years (average of 4–8 years). Rifampin and other medications make the patient noninfectious in a short time, so that ambulatory treatment is possible. Multidrug therapy (MDT) has been shown to be highly effective in combating the disease, with a very low relapse rate. Treatment with MDT ensures that the bacillus does not develop drug resistance. The increase has been associated with improved case finding. BCG may be useful in reducing tuberculoid leprosy among contacts. Investigation of contacts over 5 years is recommended.

The disease is still highly endemic primarily in five countries: India, Brazil, Indonesia, Myanmar, and Bangladesh, and is still present in some 80 countries in southeast Asia, including the Philippines and Myanmar, sub-Saharan Africa, the Middle East (Sudan, Egypt, Iran), and in some parts of Latin America (Mexico, Colombia) with isolated cases in the United States. World prevalence has declined from 10.5 million cases in 1980, 5.5 million in 1990, to fewer than 300,000 in 2004. WHO aimed to eliminate leprosy as a public health problem by 2000, defined as prevalence of fewer than 1 per 10,000 population, or fewer than 300,000 cases. The achievement of this goal has been a major historical event in public health. WHO reports that "the number of new cases detected globally has fallen by more than 40,019 cases (a 13.4 percent decrease) during 2006 compared with 2005. During the past 5 years, the global number of new cases detected has continued to decrease dramatically, at an average rate of nearly 20 percent per year," and "pockets of high endemicity still remain in some areas of Angola, Brazil, Central African Republic, Democratic Republic of Congo, India, Madagascar, Mozambique, Nepal, and the United Republic of Tanzania. These countries remain highly committed to eliminating the disease, and continue to intensify their leprosy control activities."

TRACHOMA

Trachoma is currently responsible for 6 million blind persons or 15 percent of total blindness in the world. The causative organism, *Chlamydia trachomatis,* is a bacteria

which can survive only within a cell. It is spread through contact with eye discharges, usually by flies, or household items (e.g., handkerchiefs, washcloths). Trachoma is common in poor rural areas of Central America, Brazil, Africa, parts of Asia, and some countries in the eastern Mediterranean. The resulting infection leads to conjunctival scarring and if untreated, to blindness. WHO estimates there are 148 million cases of active disease in 46 endemic countries. Hygiene, vector control, and treatment with antibiotic eye ointments or simple surgery for scarring of eyelids and inturned eyelashes prevent the blindness. A new drug, azithromycin, is effective in curing the disease. The WHO is promoting a program for the global elimination of trachoma using azithromycin and hygiene education in endemic areas.

Chlamydia (*Chlamydia pneumonia*) infection is known to be a widespread chronic risk factor for coronary artery disease. Intraarterial infection, among other contributing etiologies, contributes to plaque formation, thromboembolic occlusion of arteries, and myocardial infarction. While antibiotic treatment of chlamydias as a preventive measure for heart disease has not been used, this could potentially reduce the burden of the leading worldwide cause of death at a relatively low cost.

SEXUALLY TRANSMITTED INFECTIONS

Sexually transmitted infections (STIs) are widespread internationally with an estimated 330 million new cases per year, with 5.8 million new cases, over 30 million total cases, and 2.3 million deaths (1997). AIDS has captured world attention over the past decade. The global burden of STIs is enormous (Table 4.8), and the public health and social consequences are devastating in many countries.

Sexually transmitted infections, especially in women, may be asymptomatic, so that severe sequelae may occur before patients seek care. Infection by one STI increases risk of infection by other diseases in this group.

Syphilis

Syphilis is caused by the spirochete *Treponema pallidum*. After an incubation period of 10–90 days (mean is 21 days), primary syphilis develops as a painless ulcer or chancre on the penis, cervix, nose, mouth, or anus, lasting 4–6 weeks. The patient may first present with secondary syphilis 6–8 weeks (up to 12 weeks) after infection with a general rash and malaise, fever, hair loss, arthritis, and jaundice. These symptoms spontaneously disappear within weeks or up to 12 months later. Tertiary syphilis may appear 5–20 years after initial infection. Complications of tertiary syphilis include catastrophic cardiovascular and central nervous system conditions. Early antibiotic treatment is highly effective when given in a large initial dose, but longer-term therapy may be needed if treatment is delayed.

TABLE 4.8 Prevalence of Sexually Transmitted Infections by WHO Region, 1999

Region	Estimated cases 1999 (millions)
Australia, New Zealand	1
Southeast Asia	151
East Asia and Pacific	18
East Europe and Central Asia	22
Latin America and Caribbean	38
North America	14
Sub-Saharan Africa	69
North Africa and Middle East	10
Total All Regions	323

Sources: World Health Organization, http://www.who.int/hiv/pub/sti/who_hiv_aids_2001.02.pdf [accessed October 23, 2007]
World Health Organization, http://www.who.int/reproductive-health/publications/rtis_gep/fpmethods.htm [accessed October 23, 2007].
World Health Organization. 2001 Global prevalence and incidence of selected curable sexually transmitted diseases: Overview and estimates. Geneva: World Health Organization.

Gonorrhea

Gonorrhea (GC) is caused by the bacterium *Neisseria gonorrhoeae*. The incubation period is 1–14 days. Gonorrhea is often associated with concurrent chlamydia infection. In women, GC may be asymptomatic or it may cause vaginal discharge, pain on urination, bleeding on intercourse, or lower abdominal pain. Untreated, it can lead to sterility. In men, GC causes urethral discharge and painful urination. Treatment with antibiotics ends infectivity, but untreated cases can be infectious for months. Drug resistance to penicillin, tetracycline, and quinolones has emerged in many countries so that more expensive and often unavailable drugs are necessary for treatment. Prevention of gonococcal eye infection in newborns is based on routine use of antibiotic ointments in the eyes of newborns.

Other Sexually Transmitted Infections

Chancroid

Chancroid is caused by *Haemophilus ducreyi*. In women, chancroids may cause a painful, irregular ulcer near the vagina, resulting in pain on intercourse, urination, and defecation, but it may be asymptomatic. In men it causes a painful, irregular ulcer on the penis. The incubation period is usually 3–5 days, but may be up to 14 days. An individual is infectious as long as there are ulcers, usually 1–3 months. Treatment is by erythromycin or azithromycin.

Herpes Simplex

Herpes simplex is caused by herpes simplex virus types 1 and 2 and has an incubation period of 2–12 days. Genital herpes causes painful blisters around the mouth, vagina, penis, or anus. The genital lesions are infectious for 7–12 days. Herpes may lead to central nervous system meningoencephalitis infection. It can be transmitted to newborns during vaginal delivery, causing infection, encephalitis, and death. Cesarean delivery is therefore necessary when a mother is infected. Antiviral drugs are used in treatment, orally, topically, or intravenously.

Chlamydia

Chlamydia is caused by *Chlamydia trachomatis*. It is the most common sexually transmitted infection in the United States, where reported incidence has increased to nearly 1 million in 2005–2006. Underreporting is a major problem; actual incidence is estimated at more than twice that reported. In women, it is usually asymptomatic but may cause vaginal discharge, spotting, pain on urination, lower abdominal pain, and pelvic inflammatory disease (PID). In newborns, chlamydia may cause eye and respiratory infections. In men, chlamydia causes urethral discharge and pain on urination. The incubation period is 7–21 days and the infectious period is unknown. Treatment for chlamydia is doxycycline, azithromycin, or erythromycin. Because co-transmission with gonorrhea is extremely common, CDC recommends treatment for both diseases when either is confirmed. Chlamydia infection, not necessarily venereal in transmission, may be transmitted to newborns of infected mothers. *Chlamydia pneumoniae* is suspected and under investigation as a possible cause or contributor in coronary heart disease.

Trichomoniasis

Trichomoniasis is caused by *Trichomonas vaginalis*. The incubation period is 4–20 days (mean is 7 days). In women, trichomoniasis may be asymptomatic or may cause a frothy vaginal discharge with foul odor, and painful urination and intercourse. In men, the disease is usually mild, causing pain on urination. Treatment is by metronidazole taken orally. Without treatment, the disease may persist and remain infectious for years.

Human Papillom Virus (HPV)

HPV is endemic throughout the world and the leading cause of cervical neoplasia and cancer of the cervix. HPV includes many types associated with venereal warts (condylomas). An effective vaccine against the most common carcinogenic strains is now available and recommended for young women to prevent cervical cancer, a breakthrough of enormous importance for this is one of the leading causes of cancer mortality in women. Prevention of cervical cancer by vaccine and by Pap smear screening is a major advance in public health, along with the prevention of liver cancer by hepatitis B immunization. Circumcision is now recommended by WHO for primary prevention of transmission of HPV (see Chapters 5 and 6).

Control of Sexually Transmitted Infections

In areas where a full range of diagnostic services is lacking, a "syndromic approach" is recommended for the control of STIs. The diagnosis is based on a group of symptoms and treatment on a protocol addressing all the diseases that could possibly cause those symptoms, without expensive laboratory tests and repeated visits. Early treatment without laboratory confirmation helps to cure persons who might not return for follow-up, or may place them in a noninfective stage so that even without follow-up they will not transmit the disease. STI incidence between 1950 and 2004 is shown in Table 4.9, with decline overall except around 1990, with subsequent further fall in incidence.

Screening in prenatal and family planning clinics, prison medical services, and in clinics serving prostitutes, homosexuals, or other potential risk groups will detect subclinical cases of various STIs. Treatment can be carried out cheaply and immediately. For instance, the screening test for syphilis costs $0.10 and the treatment with benzathine penicillin injection costs about $0.40. Partner

TABLE 4.9 Reportable Sexually Transmitted Infections,[a] United States, Selected Years, 1950–2004

Disease	1950	1960	1970	1980	1985	1990	2000	2004
Syphilis (all stages)	146	69	45	31	29	54	11	12
Gonorrhea	192	145	297	445	384	278	129	114

Source: *Health United States*, 1998, 2006.
[a]The increase in syphilis in 1985–1990 and subsequent decline by more than 50 percent in reported cases includes all three stages of the disease as well as congenital syphilis. Rates are cases per 100,000 population, rounded.

notification is a controversial issue, but may be needed to identify contacts who may be the source of transmission to others.

Control of STIs through a syndrome approach based on primary care providers is being promoted by WHO. Health education directed at high-risk target groups is essential. Providing easy and cost-free access to acceptable, nonthreatening treatment is vital in promoting the early treatment of cases and thereby reducing the risk of transmission.

Promoting prevention through the use of condoms and/or monogamy requires long-term educational efforts that are now fostered by the HIV/AIDS pandemic. Increased use of condoms for HIV prevention is associated with reduced risk of other STIs. Training medical care providers in STI awareness should be stressed in undergraduate and continuing educational efforts including personal protection as caregivers.

HIV/AIDS

Human immunodeficiency virus (HIV) is a retrovirus that infects various cells of the immune system, and also affects the central nervous system. Two types have been identified: HIV1, worldwide in distribution, and the less pathogenic HIV2, found mainly in West Africa. HIV is transmitted by sexual contact, exposure to blood and blood products, perinatally, and via breast milk. The period of communicability is unknown, but studies indicate that infectiousness is high, both during the initial period after infection and later in the disease. Antibodies to HIV usually appear within 1–3 months.

Within several weeks to months of the infection, many persons develop an acute self-limited flulike syndrome. They may then be free from any signs or symptoms for months to more than 10 years. Onset of illness is usually insidious with nonspecific symptoms, including sweats, diarrhea, weight loss, and fatigue. AIDS represents the later clinical stage of HIV infection. According to the revised CDC case definition (1993), AIDS involves any one or more of the following: low CD_4 count, severe systemic symptoms, opportunistic infections such as *Pneumocystis* pneumonia or TB, aggressive cancers such as Kaposi's sarcoma or lymphoma, and/or neurologic manifestations, including dementia and neuropathy. The WHO case definition is more clinically oriented, relying less on often unavailable laboratory diagnoses for indicator diseases.

This pandemic brought home lessons of public health and hygiene that had been forgotten in a smug confidence and reliance on antimicrobial therapy and vaccines that were assumed to be capable of defeating all infectious diseases. Regrettably this is not the case, and the HIV/AIDS experience showed the price of negligence in infectious disease control of sexually transmitted infections. With no vaccine yet on the horizon, the prospects for this disease are grim and its spread certain until an effective vaccine can be developed. However, the pattern of mortality in the United States is shown in Figure 4.5 from CDC, Atlanta, indicating the potential for prolonging survival, improving quality of life and reducing transmission. Active public health measures include education on AIDS prevention and condom promotion, and effective medical care based on antiretroviral therapy (ART) and for tuberculosis and other opportunistic infections, as well as nutritional supplementation and general care, is also gaining ground as a preventive measure in sub-Saharan Africa.

AIDS was first recognized clinically in 1981 in Los Angeles and New York. By mid-1982 it was considered an epidemic in those and other U.S. cities. It was primarily seen among men who have sex with men and recipients of blood products. After initial errors, testing of blood and blood products became standard and has subsequently closed off this method of transmission. Transmission has changed markedly since the initial onslaught of the disease, with needle sharing among intravenous drug users, heterosexual activity, and maternal–fetal transmission becoming major factors. Comorbidity with other STIs apparently increases HIV infectivity and may have helped to convert the epidemiology to a greater degree of heterosexual transmission (Box 4.15 and Figure 4.5).

The disease grew exponentially in the United States but incidence of new cases has declined since 1993. AIDS is also a major public health problem in most developed and developing countries, reaching catastrophic proportions in some sub-Saharan African countries, affecting up to 30 percent or more of the population.

HIV-related deaths were the eighth leading cause of all deaths in 1993 in the United States, the leading cause among men aged 25–44 years of age, and the fourth leading cause for women in this age group. By 2005, AIDS had been diagnosed in 984,000 persons and 550,000 had died. At the end of 2003, it was estimated that up to 1.1 million persons are HIV infected in the United States. Up to 30 percent of these people may not know they are infected. In 2005, 42,000 new diagnoses were reported.

Globally, deaths from AIDS totaled 2.8 million in 2005, with an estimated 11.7 million persons having died

Box 4.15 HIV/AIDS, 1981–2006

AIDS was first reported as a clinical entity by Dr. Michael Gottlieb at the University of California Los Angeles (UCLA) Hospital. He reported in *Morbidity and Mortality Weekly Report* and later in the *New England Journal of Medicine* on five cases of *Pneumocystis carinii* (now *P. jiroveci*) pneumonia with cytomegaloviremia (CMV) among young male homosexuals with evidence of immune deficiency. A few weeks later, Dr. Alvin Friedman-Kien reported 26 cases of Kaposi's sarcoma in gay men from New York and California.

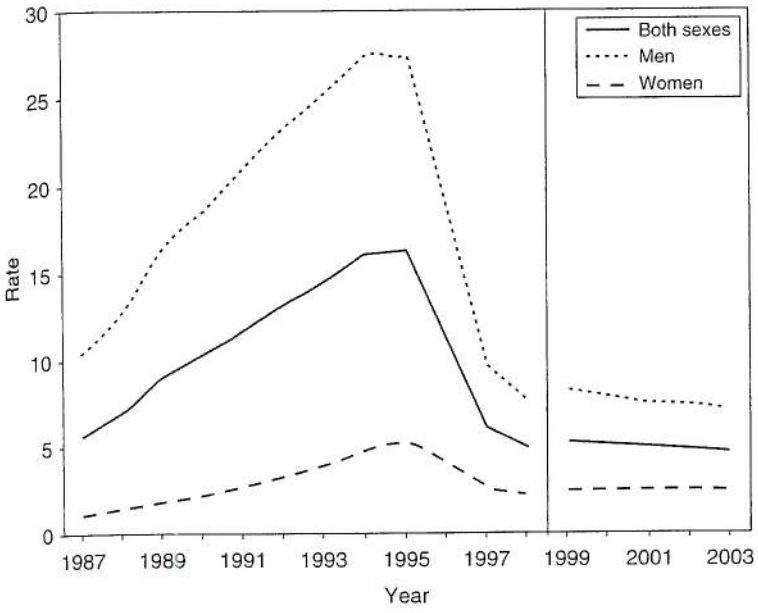


FIGURE 4.5 Age-adjusted death rates for HIV/AIDS, United States, 1987–2003. Sources: Fee, E., Brown, T. 2006. M. Michael S. Gottlieb and the identification of AIDS. *American Journal of Public Health*, 9:982–983. Stall, R., Mills, T. C. [editorial]. 2006. A quarter century of AIDS. *American Journal of Public Health*, 9:959–961. UNAIDS. 2005. AIDS Epidemic Update — December 2005. New York UNAIDS. Centers for Disease Control. 2006. Epidemiology of AIDS/HIV — United States, 1981–2005. *Morbidity and Mortality Weekly Report*, 55:589–592. Note: Definitions changed slightly in 1998.

from this pandemic up to 1997. In 2005, there were an estimated 4.1 million new cases. Due to implementation of coordinated control programs though, it is believed the pandemic expansion peaked in the late 1990s. The WHO aims to reverse the increase of HIV infection by 2015. With increased attention, training, and funding, this may be possible.

The declining incidence of new cases in industrialized nations may be the result of greater awareness of the disease and methods of prevention of transmission. Improving early diagnosis and access to care, especially the combined therapy programs that are very effective in delaying onset of symptoms, is an important part of public health management of the AIDS crisis. Until an effective vaccine is available, preventive reliance will continue to be on behavior risk reduction and other prevention strategies such as needle and condom distribution among high-risk population groups.

Throughout the world, HIV continues to spread rapidly, especially in poor countries in Africa, Asia, and South and Central America. The United Nations reports that 40 million persons are living with HIV/AIDS, 90 percent of them in developing countries, where transmission is largely by heterosexual contact. Every day, more than 8500 persons are infected including 1000 children. In Thailand, 1 person in 50 is now infected. In sub-Saharan Africa more than 1 in 40 is infected and in some cities as many as 1 in 3 people carry the virus. Estimations of new infections per year in sub-Saharan Africa range from 1 to 2 million persons, while in Asia the range is from 1.2 to 3.5 million new infected persons per year. Lessons are still being learned from the AIDS pandemic. The explosive spread of this infection, from an estimated 100,000 people in 1980 to an anticipated 40 million persons HIV infected, shows that the world is still vulnerable to pandemics of emerging infectious diseases. Enormous movements of tourists, businesspeople, truck drivers, migrants, soldiers, and refugees promote the spread of such diseases. Widespread sexual exchange, traffic in blood products, and illicit drug use all promote the international potential for pandemics. War and massive refugee situations promote rape and prostitution, worsening the AIDS situation in some settings in Africa.

The HIV pandemic has spread throughout the world. However, there is the somewhat hopeful indication that the rate of increase has slowed in the United States. This may be an indication of a number of factors; higher levels of self-protective behavior; the most susceptible population groups have already been affected; and the spread into the general population is at a slower rate. It is also possible that this may yet prove to be only a lull in the storm, as heterosexual contact becomes a more important mode of transmission.

The UNAIDS 2006 report showed signs that combinations of several drugs from among a number of antiretroviral medications are showing promise to suppress the AIDS virus in infected people. At a current annual price of nearly $20,000 per patient, these sums are well beyond the capacity of most developing countries. Development of methods of measuring the HIV viral load have allowed for better evaluation of potential therapies and monitoring of patients receiving therapy. In developed countries, transmission by blood products has been largely controlled by screening tests, transmission among homosexuals has been reduced by safe sex practices, and transmission to newborns has been reduced by recent therapeutic advances. Safe sex practices and condom use may have helped in reducing heterosexual transmission. Further

advances in therapy and prevention with a vaccine are expected over the next decade.

The HIV/AIDS pandemic is one of the great challenges to public health for the twenty-first century due to its complexity; its international spread; its sexual and other modes of transmission; its devastating and costly clinical effects; and its impact on parallel diseases such as tuberculosis, respiratory infections, and cancer. The cost of care for the AIDS patient can be very high. Needed programs include home care and community health workers to improve nutrition and self-care, and mutual help among HIV carriers and AIDS patients. The ethical issues associated with AIDS are also complex regarding screening of pregnant women, newborns, partner notification, reporting, and contact tracing, as well as financing the cost of care.

DIARRHEAL DISEASES

Diarrheal diseases are the leading cause of child mortality in the world. They are caused by a wide variety of bacteria, parasites, and viruses (Table 4.10) infecting the intestinal tract and causing secretion of fluids and dissolved salts into the gut with mild to severe or fatal complications.

In developing countries, diarrheal diseases account for half of all morbidity and a quarter of all mortality. Diarrhea itself does not cause death, but the dehydration resulting from fluid and electrolyte loss is one of the most common causes of death in children worldwide. Deaths from dehydration can be prevented by use of oral rehydration therapy (ORT), an inexpensive and simple method of intervention easily used by a nonmedical primary care worker and by the mother of the child as a home intervention. In 1983, diarrheal diseases were the cause of almost 4 million child deaths, but by 1996 this had declined to 2.4 million, largely under the impact of increased use of ORT.

Diarrheal diseases are transmitted by water, food, and directly from person to person via oral–fecal contamination. Diarrheal diseases occur in epidemics in situations of food poisoning or contaminated water sources, but can also be present at high levels when common source contamination is not found. Contamination of drinking water by sewage and poor management of water supplies are also major causes of diarrheal disease. The use of sewage for the irrigation of vegetables is a common cause of diarrheal disease in many areas.

TABLE 4.10 Major Organisms Associated with Diarrheal Diseases

Classification	Organisms
Bacteria	*Salmonella, Shigella, Escherichia coli, Vibrio cholerae, Bacillus cereus, Campylobacter jejuni*
Virus	Enteroviruses, rotaviruses, adenoviruses, astroviruses, calciviruses, coronaviruses, small round virus group, Norwalk group
Parasites/ Protozoa	*Schistosoma, Giardia lamblia*, cryptosporidium, *Amoeba histolytica*

Salmonella

Salmonella are a group of bacterial organisms causing acute gastroenteritis, associated with generalized illness including headache, fever, abdominal pains, and dehydration. There are over 2000 serotypes of *Salmonella*, many of which are pathogenic in humans, the most common of which are *Salmonella typhimurium, S. enteritidis,* and *S. typhi*. Transmission is by ingestion of the organisms in food, derived from fecal material from animal or human contamination. Common sources include raw or uncooked eggs, raw milk, meat, poultry and its products, as well as pet turtles or chicks. Fecal–oral transmission from person to person is common. Prevention is in safe animal and food handling, refrigeration, sanitary preparation and storage, protection against rodent and insect contamination, and the use of sterile techniques during patient care. Antibiotics rarely affect disease progression and may lead to increased carrier rates and produce resistant strains; therefore only symptomatic and supportive treatment is recommended, except in systemic and life-threatening cases.

S. typhi causes typhoid fever and is estimated by WHO to kill some 500,000 persons per year and seriously affect millions of others. While treatable by ampicillin and fluid replacement, the antibiotics are becoming less effective. Two vaccines are currently available and are used in high-risk areas.

Shigella

Shigella are a group of bacteria that are pathogenic in man. The infectious dose of *Shigella* is among the lowest of all pathogens; fewer than 10 organisms are sufficient to cause disease within four groups: type A– (*Shigella dysenteriae*), type B– (*S. flexneri*), type C– (*S. boydii*), and type D– (*S. sonnei*). Types A, B, and C are each further divided into a total of 40 serotypes. *Shigella* are transmitted by direct or indirect fecal–oral methods from a patient or carrier, and illness follows ingestion of even a few organisms. Water and milk transmission occurs as a result of contamination. Flies can transmit the organism, and in nonrefrigerated foods the organism may multiply to an infectious dose. Control is in hygienic practices and in the safe handling of water and food. *Shigella* is a common cause of waterborne disease outbreaks where water supplies are contaminated and not treated adequately.

Escherichia coli

E. coli are common fecal contaminants of inadequately prepared and cooked food. Particularly virulent strains such as O157:H17 can cause explosive outbreaks of severe (enterohemorrhagic) diarrheal disease with a hemolytic-uremic syndrome and death, as occurred in Japan in 1998 with cases and deaths due to a food-borne epidemic. Sporadic, but significant epidemics occur often, mostly in developed countries where food processing and transport are common. Other milder strains cause traveler's diarrhea and nursery infections. Inadequately cooked hamburger, unpasteurized milk, and other food vectors are discussed under "Food Safety" in Chapter 8. However, food-borne disease occurs in developed countries as well as in the case of contaminated lettuce from California in 2007.

Cholera

Cholera is an acute bacterial enteric disease caused by *Vibrio cholerae*, with sudden onset, profuse painless watery stools, occasional vomiting, and if untreated, rapid dehydration, circulatory collapse, and death. Similar disease may be caused by other "cholerogenic" species of *Vibrio*. Asymptomatic infection or carrier status, and mild cases are common. In severe, untreated cases, mortality is over 50 percent, but with adequate treatment, mortality is under 1 percent. Diagnosis is based on clinical signs, epidemiologic, serologic, and bacteriologic confirmation by culture. The two types of cholera are the classic and el Tor (with Inaba and Ogawa serotypes).

In 1991, a large-scale epidemic of cholera spread through much of South America. It was imported via a Chinese freighter, whose sewage contaminated shellfish in Lima harbor in Peru (Box 4.16). Epidemics in South America, south Asia, and Iraq have caused hundreds of thousands of cases and thousands of deaths since 1991.

Prevention requires sanitation, particularly the chlorination of drinking water; prohibiting the use of raw sewage for the irrigation of vegetable crops; and high standards of community, food, and personal hygiene. Crucial treatment is prompt fluid therapy with electrolytes in large volume to replace all fluid loss with oral rehydration therapy (ORT). Tetracycline shortens the duration of the disease, and chemoprophylaxis for contacts following stool samples may help in reducing its spread. A vaccine is available but is of no value in the prevention of outbreaks.

Viral Gastroenteritis

Viral gastroenteritis can occur in sporadic or epidemic forms, in infants, children, or adults. Some viruses, such as the rotaviruses and enteric adenoviruses, affect mainly infants and young children, and may be severe enough to cause hospitalization for dehydration. Others such as Norwalk and Norwalk-like viruses affect older children and adults in self-limited acute gastroenteritis in family, institution, or community outbreaks.

Box 4.16 The Cholera Pandemic in South America, 1991–1998

In the 1980s, Peruvian officials stopped the chlorination of community water supplies because of concern over possible carcinogenic effects of trihalomethanes, a view encouraged by officials of the U.S. Environmental Protection Agency (EPA) and the U.S. Public Health Service. In January 1991, a Chinese freighter arrived in Lima, Peru, and dumped bilge (sewage) in the harbor, apparently contaminating local shellfish. Consumption of raw shellfish is a popular local delicacy (ceviche) and is associated with cases of cholera seen in local hospitals.

Contamination of local water supplies from sewage resulted in the geometric increase in cases, and by the end of 1992, the Pan American Health Organization (PAHO) reported an epidemic of 391,000 cases and 4002 deaths. The epidemic spread to 21 countries, and in 1992 there were a further 339,000 cases and 2321 deaths spreading over much of South America, continuing in 1999.

In the United States, 102 cases of cholera were reported in 1992; of these, 75 cases and 1 death were among passengers of an airplane flying from South America to Los Angeles in which contaminated seafood was served. In 1993, 91 cases of cholera were reported in the United States which were unrelated to international travel. These occurred mostly among persons consuming shellfish from the Gulf coast with a strain of cholera similar to the South American strain, also possibly introduced in a ship ballast. Cholera organisms are reported in harbor waters in other parts of the United States.

Sources: Anderson, C. 1991. Cholera epidemic traced to risk miscalculation. *Nature*, 354:255. Centers for Disease Control. 1993. Update cholera Western — hemisphere, 1992. MMWR, 42:89–91. Centers for Disease Control. 1993. Isolation of *Vibrio cholerae* O1 from Oysters — Mobile Bay, 1991–1992. *MMWR*, 42:91–93.

Rotaviruses

Rotaviruses cause acute gastroenteritis in infants and young children, with fever and vomiting, followed by watery diarrhea and occasionally severe dehydration and death if not adequately treated. Diagnosis is by examination of stool or rectal swabs with commercial immunologic kits. In both developed and developing countries, rotavirus is the cause of about one-third of all hospitalized cases for diarrheal diseases in infants and children up to age 5. Most children in developing countries experience this disease by the age of 4 years, with the majority of cases between 6 and 24 months. In developing countries, rotaviruses are estimated to cause over 1 million deaths per year. The virus is found in temperate climates in the

cooler months and in tropical countries throughout the year. Breastfeeding does not prevent the disease but may reduce its severity. Oral rehydration therapy is the key treatment. A live attenuated vaccine was approved by the FDA in 1998 and adopted in the 1999 U.S. recommended routine vaccination programs for infants.

Adenoviruses

Adenoviruses, Norwalk, and a variety of other viruses (including astrovirus, calcivirus, and other groups) cause sporadic acute gastroenteritis worldwide, mostly in outbreaks. Spread is by the oral–fecal route, often in hospital or other communal settings, with secondary spread among family contacts. Food-borne and waterborne transmission are both likely. These can be a serious problem in disaster situations. No vaccines are available. Management is with fluid replacement and hygienic measures to prevent secondary spread.

Parasitic Gastroenteritis

Giardiasis

Giardiasis (caused by *Giardia lamblia*) is a protozoan parasitic infection of the upper small intestine, usually asymptomatic, but sometimes associated with chronic diarrhea; abdominal cramps; bloating; frequent, loose, greasy stools; fatigue; and weight loss. Malabsorption of fats and vitamins may lead to malnutrition. Diagnosis is by the presence of cysts or other forms of the organism in stools, duodenal fluid, or in intestinal mucosa from a biopsy. This disease is prevalent worldwide and affects mostly children. It is spread in areas of poor sanitation and in preschool settings and swimming pools, and is of increasing importance as a secondary infection among immunocompromised patients, especially those with AIDS.

Waterborne giardia was recognized as a serious problem in the United States in the 1980s and 1990s, since the protozoa are not readily inactivated by chlorine, but require adequate filtration before chlorination. Person-to-person transmission in day-care centers is common, as is transmission by unfiltered stream or lake water where contamination by human or animal feces is to be expected. An asymptomatic carrier state is common. Prevention relies on careful hygiene in settings such as day-care centers, filtration of public water supplies, and the boiling of water in emergency situations.

Cryptosporidium

Cryptosporidium parvum is a parasitic infection of the gastrointestinal tract in man, small and large mammals, and vertebrates. Infection may be asymptomatic or cause a profuse, watery diarrhea, abdominal cramps, general malaise, fever, anorexia, nausea, and vomiting. In immunosuppressed patients, such as persons with AIDS, it can be a serious problem. The disease is most common in children under 2 years of age and those in close contact with them, as well as in homosexual men. Diagnosis is by identification of the *Cryptosporidium* organism cysts in stools. The disease is present worldwide. In Europe and the United States, the organism has been found in 1 to 4.5 percent of individuals sampled. Spread is common by person-to-person contact by fecal–oral contamination, especially in such settings as day-care centers. Raw milk and waterborne outbreaks have also been identified in recent years. A large waterborne disease outbreak due to *Cryptosporidium* occurred in Milwaukee in 1986 as described in Chapter 9. Management is by rehydration and prevention is by careful hygiene in food and water safety.

Helicobacter pylori

Helicobacter pylori, first identified in 1986, is a bacterium causally linked to gastrointestinal ulcers and gastritis, contributing to high rates of gastric cancer (Chapter 5). It is an important example of the link between infection and chronic disease. This has enormous implications for prevention of cancer of the stomach, chronic peptic ulcers, and large-scale use of hospitals and other medical resources (see Chapter 5).

A Program Approach to Diarrheal Disease Control

The control of diarrheal diseases requires a comprehensive program involving a wide range of activities, including good management of food and water supplies, education in hygiene, and, particularly where morbidity and mortality are high, education in the use of oral rehydration therapy (ORT).

Oral rehydration therapy (ORT) is considered by UNICEF and WHO to have resulted in the saving of 1 million lives each year in the 1990s. Proper management of an episode of diarrhea by ORT (Box 4.17), along with continued feeding, not only saves the child from dehydration and immediate death, but also contributes to early restoration of nutritional adequacy, sparing the child the prolonged effects of malnutrition.

The World Summit for Children (WSC) in 1990 called for a reduction in child deaths from diarrheal diseases by one-third and malnutrition by one-half, with emphasis on the widest possible availability, education for, and use of ORT. This requires a programmatic approach. Public health leadership must train primary care doctors, pediatricians, pharmacists, drug manufacturers, and primary care health workers of all kinds in ORT principles and usage. They must be backed by the widest possible publicity to raise awareness among parents.

Box 4.17 WHO Formula for Oral Rehydration Therapy (ORT)

Ingredients	Amounts in grams/liter	Ions	Concentration (millimoles/liter)
Sodium chloride, NaCl	3.5	Sodium	90
Trisodium citrate, dihydrate, or sodium bicarbonate $NaHCO_3$	2.9 or 2.5	Citrate*	20 citrate**
Potassium chloride, KCl	1.5	Potassium	10 of potassium, 80 of chloride
Glucose (anhydrous)	20.0	Glucose	111

*Note: or 2.5 grams sodium bicarbonate.
**or 30 millimole bicarbonate.
Sources: World Health Organization. 1992. *Readings on Diarrhoea: Student Manual*, Geneva: World Health Organization. Heymann, D. L. (ed.). 2004. *Control of Communicable Diseases Manual*, 18th ed. Washington, DC: American Public Health Association.

Oral rehydration therapy is an important public health modality in developed countries as well as in developing countries. Diarrheal disease may not cause death as frequently in developed countries, but it is still a significant factor in infant and child health and, even under the most optimal conditions, can cause setbacks in the nutritional state and physical development of a child. Use of ORT does not prevent the disease (i.e., it is not a primary prevention), but it is excellent in secondary prevention, by preventing complications from diarrhea, and should be available in every home for symptomatic treatment of diarrheal diseases.

An adaptation of ORT has found its place in popular culture in the United States. A form of ORT, marketed as "sports drinks," is used in sports where athletes lose large quantities of water and salts in sweat and insensible loss from the respiratory tract. The wider application of the principles of ORT for use in adults in dry hot climates and in adults under severe physical exertion with inadequate fluid/salt intake situations requires further exploration.

Management of diarrheal diseases should be part of a wider approach to child nutrition. The child who goes through an episode of diarrheal disease may falter in growth and development. Supportive measures may be needed following the episode as well as during it. This involves providing primary care services that are attuned to monitoring individual infant and child growth. Growth monitoring surveillance is important to assess the health status of the individual child and the child population. Supplementation of infant feeding with vitamins A and D, and iron to prevent anemia are important for routine infant and child care, and more so for conditions affecting total nutrition such as a diarrheal disease.

ACUTE RESPIRATORY INFECTIONS

In the developing world, respiratory infections account for over one-quarter of all deaths and illnesses in children. As diarrheal disease deaths are reduced, the major cause of death among infants in developing countries is becoming acute respiratory infections (ARIs). In industrialized countries, ARIs are important for their potentially devastating effects on the elderly and chronically ill. They are also the major cause of morbidity in infants in developed countries, causing much anxiety to parents even in areas with good living conditions. Cigarette smoking, chronic bronchitis, poorly controlled diabetes or congestive heart failure, and chronic liver and kidney disease increase susceptibility to ARIs. ARIs place a heavy burden on health care systems and individual families. Improved methods of management of such chronic diseases are needed to reduce the associated toll of morbidity, mortality, and the considerable expenses of health care.

Acute respiratory infections are due to a broad range of viral and bacterial infections. Secondary bacterial infections progress to pneumonia with mortality rates of 10–20 percent. Acute viral respiratory diseases include those affecting the upper respiratory tract, such as acute viral rhinitis, pharyngitis, and laryngitis, as well as those affecting the lower respiratory tract, tracheobronchitis, bronchitis, bronchiolitis, and pneumonia. ARIs are frequently associated with VPDs, including measles, varicella, and influenza. They are caused by a large number of viruses, producing a wide spectrum of acute respiratory illness. Some organisms affect any part of the respiratory tract, while others affect specific parts and all predispose to bacterial secondary infection. While children and the elderly are especially susceptible to morbidity and mortality from acute respiratory disease, the vast numbers of respiratory illnesses among adults cause large-scale economic loss from work absence.

Bacterial agents causing upper respiratory tract infection include group A *Streptococcus, Mycoplasma pneumoniae,* pertussis, and parapertussis. Pneumonia or acute bacterial infection of the lower respiratory tract and lung tissue may be due to pneumococcal infection with

Streptococcus pneumoniae. There are 83 known types of this organism, distinguished by capsule characteristics; 23 account for 88 percent of pneumococcal infections in the United States. An excellent polyvalent vaccine based on these types is available for high-risk groups such as the elderly; immunodeficient patients; and persons with chronic heart, lung, liver, blood disorders, or diabetes.

Opportunistic infections attack the chronically ill, especially those with compromised immune systems, often with life-threatening ARIs. Mycoplasma (primary atypical pneumonia) is a lower respiratory tract infection which sometimes progresses to pneumonia. TB and *Pneumonocytis jiroveci* are especially problematic for AIDS patients. Other organisms causing pneumonias include *Chlamydia pneumoniae, H. influenzae, Klebsiella pneumonia, Escherichia coli, Staphylococcus,* rickettsia (Q fever), and *Legionella*. Parasitic infestation of lungs may occur with nematodes (e.g., ascariasis). Fungal infections of the lung may be caused by aspergillosis, histoplasmosis, and coccidiomycosis, often as a complication of antibiotic therapy.

Access to primary care and early institution of treatment are vital to control excess mortality from ARIs. In developed countries, ARIs as contributors to infant deaths are largely a problem in minority and deprived population groups. Because these groups contribute disproportionately to childhood mortality, infant mortality reduction has been slower in countries such as the United States and Russia than in other industrialized countries. The continuing gap in mortality rates between white and African-American children in the United States can, to a large extent, be attributed to ARIs and less access to organized primary care. Children are brought to emergency rooms for care when the disease process is already advanced and more dangerous than had it been attended to professionally earlier in the process. Many field trials of ARI prevention programs have proved successful, involving parent education and training of primary care workers in early assessment and, if necessary, initiation of treatment. This needs field testing in multiple settings.

Reliance on vaccines to prevent respiratory infectious diseases is not currently feasible. ARIs are caused by a very wide spectrum of viruses, and the development of vaccines in this field has been slow and limited. The vaccine for pneumococcal pneumonia has been an important breakthrough, but it is still inadequately utilized by the chronically ill because of its limitations, costs, and lack of sufficient political and public awareness, and it is too expensive for developing countries. This vaccine is recommended for infants in the United States and many industrial nations and recommended by WHO for developing countries, but as yet not widely applied in the latter. Improvements in bacterial and viral vaccine development will potentially help to reduce the burden of ARIs. A programmatic approach with clinical guidelines and education of family and caregivers is currently the only feasible way to reduce the still enormous morbidity and mortality from ARIs on the young and the elderly.

INEQUALITIES IN CONTROL OF COMMUNICABLE DISEASES

As in other fields of public health, there are wide variations or inequities between and within countries in control of communicable diseases. The differences between the industrialized countries and the developing countries are enormous. The gaps are not only in coverage, but in the content of the immunization programs. Adoption of Hib vaccine is increasing but the decade-long gap from availability to widespread global usage costs very many preventable deaths. Similarly the lag in adoption of pneumococcal pneumonia and rotavirus vaccines will prolong the time to achive the Millenium Development Goals of reducing child mortality in very many countries.

Even in the European region, there are wide differences between groups of countries as seen in Figure 4.6, comparing standardized mortality rates (3-year moving averages) for infectious and parasitic disease between long-standing members of the European Union (such as France, Germany, the United Kingdom), with the new members (since 2004, such as Hungary, Poland, and other countries of the eastern Europe) with those of the Commonwealth of Independent States (e.g., Ukraine, Russia), and finally the Central Asian Republics (e.g., Kazakhstan, Uzbekistan, Tajikistan). The trends show low and stable rates in the countries of Western and Eastern Europe, high and falling rates in Central Asia, but high and rising rates in the key countries of the former Soviet Union. While there may be artifacts of reporting, the trends are thought to be correct, and are likely to be related to many factors such as water and food safety, obsolescent immunization programs, tuberculosis and HIV control, and many other factors. Comparisons within countries will also show social and regional disparities which constitute failings of public health systems, and indicate that communicable diseases are very much part of the modern public health agenda.

The European region, which includes all of these countries, does not have a standard recommended immunization schedule and each country follows its own patterns. The western countries are generally up-to-date with the content of their programs with high coverage but this is not uniformly so in all parts of the region. The countries of the former Soviet Union are slowly updating their immunization schedules but remain largely at least a decade behind. WHO's advisory committee system on immunization has been updating their recommendations rapidly in recent years with hepatitis B, more recently Hib and pneumococcal pneumonia and adopting of the two-dose policy of MMR. As new vaccines become available, the transitional and

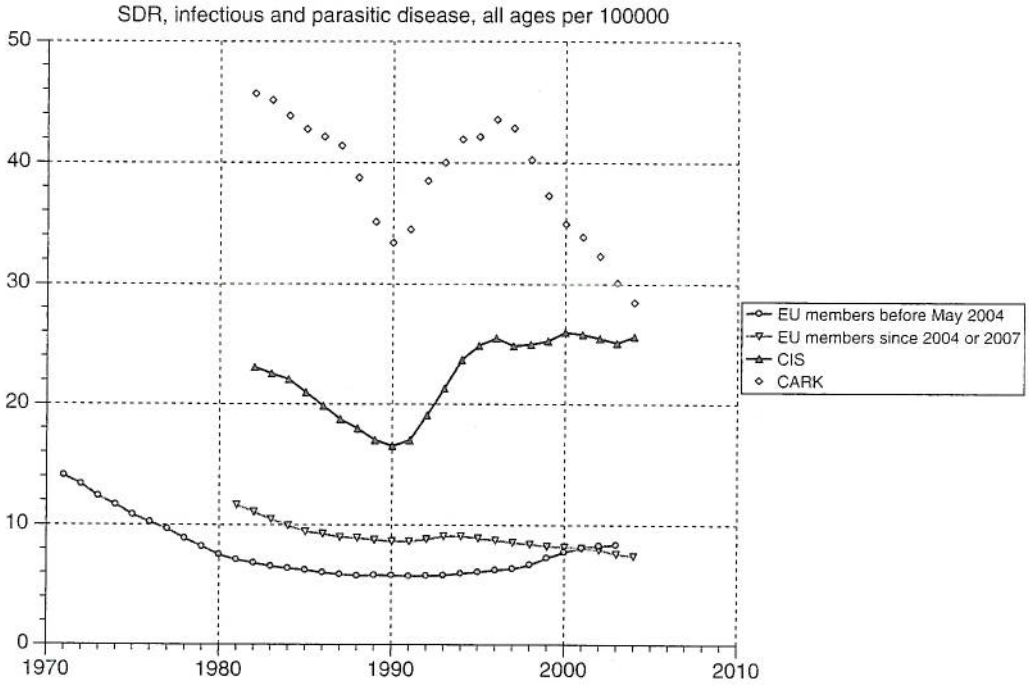


FIGURE 4.6 Standardized death rates from infectious and parasitic diseases, selected regions of Europe, 1970–2005. Source: WHO European Regional Office, Health for All Database, June 2007, www.who/dk/hfadb [accessed October 3, 2007]. Note: Rates per 100,000 population and standardized to European population.

developing countries will need support to expand their programs of immunization, a key part of the drive to attain the Millennium Development Goals of reduced child mortality and control of infectious diseases (malaria, HIV, and others).

COMMUNICABLE DISEASE CONTROL IN THE NEW PUBLIC HEALTH

The success of sanitation, vaccines, and antibiotics led many to assume that all infectious diseases would sooner or later succumb to public health and medical technology. Unfortunately, this is a premature and even dangerous assumption. Despite the long-standing availability of an effective and inexpensive vaccine, the persistence of measles as a major killer of 1 million children per year represents a failure in effective use of both the vaccine and the health system. The resurgence of TB and malaria have led to new strategies, such as managed or directly observed care, with community health workers to assure compliance needed to render the patient noninfectious to others and to reduce the pool of carriers of the disease.

Successes achieved in reducing poliomyelitis, measles, dracunculiasis, onchocerciasis, and other diseases to the point of local or global eradication have raised hopes for similar success in other fields. But there are many infectious diseases of importance in developed and developing countries where existing technologies are not fully utilized. Oral rehydration therapy (ORT) is one of the most cost-effective methods of preventing excess mortality from ordinary diarrheal diseases, and yet is not used on sufficient scale.

Biases in the financing and management of medical insurance programs can result in underutilization of available effective vaccines. Hospital-based infections cause large-scale increases in lengths of stay and expenditures, although application of epidemiologic investigation and improved quality in hospital practices could reduce this burden. Control of the spread of AIDS using combined medical therapies is not financially or logistically possible in many countries, but education for "safe sex" is effective. Community health worker programs can greatly enhance tuberculosis, malaria, and STI control, or in AIDS care, promote prevention and appropriate treatment.

In the industrialized and mid-level developing countries, epidemiologic and demographic shifts have created new challenges in infectious disease control. Prevention and early treatment of infectious disease among the chronically ill and the elderly is not only a medical issue, it is also an economic one. Patients with chronic obstructive lung disease (COPD), chronic liver or kidney disease, or congestive heart failure are at high risk of developing an infectious disease followed by prolonged hospitalization.

SUMMARY

Public health has addressed, and will continue to stress, the issues of communicable disease as one of its key issues in protecting individual and population health. Methods of intervention include classic public health through sanitation, safe water and foods, immunization, and well beyond that into nutrition, education, case finding, treatment, and changing human behavior. The knowledge, attitudes, beliefs, and practices of policymakers, health care providers, and parents are as important in the success of communicable disease control as are the technology available and methods of financing health systems. Together, these encompass the broad programmatic approach of the New Public Health to control of communicable diseases.

In a world of rapid international transport and contact between populations, systems are needed to monitor the potentially explosive spread of pathogens that may be transferred from their normal habitat. The potential for the international spread of new or reinvigorated infectious diseases constitutes threat to mankind akin to ecological and other man-made disasters.

The eradication of smallpox paved the way for the eradication of poliomyelitis, and perhaps measles, in the foreseeable future. New vaccines are showing the capacity to reduce important morbidity from rubella syndrome, mumps, meningitis, and hepatitis. Other new vaccines on the horizon will continue the immunologic revolution into the twenty-first century.

As the triumphs of control or elimination of infectious diseases of children continue, the scourge of HIV infection continues with distressingly slow progress on development of an effective vaccine or cure for the disease it engenders. Partly as a result of HIV/AIDS, TB staged a comeback in many countries where it was thought to be merely a residual problem. At the same time an old/new method of intervention using directly observed short-term therapy has shown great success in controlling the TB epidemic. The resurgence of TB is more dangerous in that MDRTB has become a widespread problem. This issue highlights the difficulty of keeping ahead of drug resistance in the search for new generations of antibiotics, posing a difficult challenge for the pharmaceutical industry, basic scientists, as well as public health workers.

The burden of infectious diseases has appeared to recede as the predominant public health problem in the developed countries but new challenges of emerging infectious diseases have come to the fore in public health, and communicable disease remains a dominating problem in the developing countries. With increases in longevity and increased importance of chronic disease in the health status of the industrial and mid-level developing nations, the effects of infectious disease on the care of the elderly and chronically ill are of great importance in the New Public Health. Long-term management of chronic disease needs to address the care of vulnerable groups, promoting the use of existing vaccines and antibiotics. Most important is the development of health systems that provide close monitoring of groups at special risk for infectious disease, especially patients with chronic diseases, the immunocompromised, and the elderly. The combination of traditional public health with direct medical care needed for effective control and eradication of communicable diseases is an essential element of the New Public Health. The challenge is to apply a comprehensive approach and management of resources to define and reach achievable targets in communicable disease control.

Control of communicable diseases is fundamental pillar of public health. The new capacities of vaccines and other methods of control develop slowly, and the advent of effective vaccines for HIV, malaria, and tuberculosis will bring untold benefit to the global community. The challenges of natural dispersion of communicable disease can be made more threatening because of the advent of bioterrorism and the emergence of new diseases or spread of those previously localized in a previously less mobile globalized world. The challenges, the potential for harm, and the benefits that can be achieved in this aspect of public health are enormous.

ELECTRONIC RESOURCES

Access to e-mail and the Internet are vital to current practice of public health and nowhere is this more important than in communicable diseases. There are many such information sites and these will undoubtedly expand in the coming years. Several sites are given as examples. The Internet has great practical implications for keeping up-to-date with rapidly occurring events and new epidemiologic and other scientific advances in this field.

Centers for Disease Control. 2006. Reported Tuberculosis in the United States, 2005. Atlanta, GA: DHHS, http://www.cdc.gov/tb/surv/surv2005/PDF/TBSurvFULLReport.pdf

Eurosurveillance Weekly. Infectious disease early warning system. http://www.eurosurveillance.org/ [accessed May 4, 2008]

Morbidity and Mortality Weekly Reports. http://www.cdc.gov [accessed May 4, 2008]

Rollback Malaria Partnership, http://www.rollbackmalaria.org [accessed June 3, 2008]

Weekly Epidemiologic Bulletin. http://www.who.ch/programmes/emc/news.htm (ProMed subscription available at http://www.isid.org/promedmail/subscribe.lasso) [accessed May 5, 2008]

World Health Organization. 2008. Avian influenza, http://www.who.int/csr/disease/avian_influenza/en/ [accessed May 4, 2008]

World Health Organization. 2008. BCG vaccine, http://www.who.int/biologicals/areas/vaccines/bcg/en/ [accessed May 4, 2008]

World Health Organization. 2008. Cholera, http://www.who.int/topics/cholera/control/en/ [accessed May 4, 2008]

World Health Organization. Dengue. http://www.who.int/csr/disease/dengue/en/ [accessed May 4, 2008]

World Health Organization. 2008. Immunization, vaccines, and biologicals, http://www.who.int/immunization/en/ [accessed May 4, 2008]

World Health Organization. 2008. Leprosy, http://www.who.int/immunization/sage_page/en/index.html [accessed May 4, 2008]

World Health Organization, MDG6: Combat HIV/AIDS, Malaria, and other diseases, http://www.who.int/topics/millennium_development_goals/diseases/en [accessed June 3, 2008]

World Health Organization, Yellow Fever, 2008, http://www.who.int/topics/yellow_fever/en

World Health Organization. 2008. Malaria, http://www.who.int/topics/malaria/en/ [accessed May 4, 2008]

World Health Organization. Neglected tropical diseases, http://www.who.int/neglected_diseases/en/ [accessed May 4, 2008]

World Health Organization. 2008. Lassa Fever, http://www.who.int/csr/disease/lassafever/en/ [accessed 3 May 2008]

World Health Organization. Zoonoses, http://www.who.int/zoonoses/en/

World Health Organization. Global malaria control and elimination, http://www.who.int/malaria/pages/elimination/malariaeliminationrec.html; http://www.who.int/malaria/docs/ReportGFImpactMalaria.pdf; http://rbm.who.int/unitedagainstmalaria/malaria/ [accessed May 3, 2008]

RECOMMENDED READINGS

Brooks, G. E., et al. 2007. *Jawetz, Melnick and Adelberg's Medical Microbiology*, 24th ed. Stamford, CT: Appleton & Lange.

Centers for Disease Control. 1999. Achievements in public health, 1900–1999: Control of infectious diseases. *Morbidity and Mortality Weekly Report*, 48:621–629.

Centers for Disease Control. 2006. *Community Guide to Preventive Services*. Multiple interventions implemented in combination are recommended to increase coverage of targeted vaccine coverage. Community Guide@CDC.gov [accessed October 30, 2007]

Centers for Disease Control. 2007. Summary of notifiable diseases — United States, 2005. *Morbidity and Mortality Weekly Report*, 54:2–92.

Centers for Disease Control. 2006. Vaccine preventable deaths and the global immunization vision and strategy, 2006–2015. *Morbidity and Mortality Weekly Report*, 55:511–515.

Centers for Disease Control and Prevention. 2007. Recommended immunization schedules for persons aged 0–18 years — United States, 2007. *Morbidity and Mortality Weekly Report Recommendations and Reports*, 5:55:Q1–4.

Cohen, J., Powderly, W. G. 2004. *Cohen & Powderly: Infectious Diseases*, 2nd ed. New York: Mosby.

Colditz, G. A., Brewer, T. F., Berkey, C. S., Wilson, M. E., Burdick, E., Fineberg, H. V., Mosteller, F. 1994. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *Journal of the American Medical Association*, 271:698–702.

Cook, G. C. 2002. *Manson's Tropical Diseases*, 21st ed. London: W. B. Saunders.

Heymann, D. L. 2004. *Control of Communicable Diseases Manual*, 18th ed. Washington, DC: American Public Health Association.

Mandel, G. L. 1994. *Principles and Practice of Infectious Diseases*. Edinburgh: Churchill-Livingstone.

Milstein, J., Cash, R. A., Wecker, J., Wikler, D. Development of priority vaccines for disease-endemic counties: Risks-benefits. *Health Affairs*, 24:718–728.

National Center for Health Statistics. 2006. *Health, United States, 2006. With Chartbook on Trends in the Health of Americans*. Hyattsville, MD: U.S. Department of Health and Human Services.

Plotkin, S. A., Orenstein, W. A. 2003. *Vaccines*, 4th ed. Atlanta: W. B. Saunders.

Stern, A. M., Markel, H. 2005. The history of vaccines and immunization: Familiar patterns, new challenges. *Health Affairs*, 24:611–621.

Thacker, S. B. 2006. Epidemiology and Public Health at CDC. *Morbidity and Mortality Weekly Report*, 55(SUP02):3–4.

Tierney, L. M., McPhee, S. J., Papadakis, M. A. 2006. *Current Medical Diagnosis & Treatment 2007*, 46th ed. New York: McGraw-Hill.

World Health Organization. 2007. *WHO Interim Protocol: Rapid Operations to Contain the Initial Emergence of Pandemic Influenza*, updated October 2007 http://www.who.int/csr/disease/avian_influenza/guidelines/draftprotocol/en/print.html [accessed October 30, 2007] .

World Health Organization. Hepatitis, http://www.who.int/csr/disease/hepatitis/whocdscsredc2007/en/index5.html

World Health Organization. Hepatitis B, WHO http://www.who.int/mediacentre/factsheets/fs204/en/

CDC. http://www.cdc.gov/ncidod/diseases/hepatitis/recs/index.htm, http://www.cdc.gov/ncidod/diseases/hepatitis/resource/PDFs/disease_burden.pdf

CDC. Hepatitis C, http://www.cdc.gov/mmwr/preview/mmwrhtml/00055154.htm; http://www.newscientist.com/channel/health/dn13539-hepatitis-c-is-first-target-for-new-therapy.html

WHO. http://www.who.int/mediacentre/factsheets/fs164/en/

World Health Organization. TB. WHO http://www.who.int/tb/en/

WHO. Strengthening the Global Response to XDR-TB. http://whqlibdoc.who.int/hq/2007/WHO_HTM_TB_2007.387_eng.pdf; http://www.who.int/tb/features_archive/drsreport_launch_26feb08/en/index.html, February 2008 [accessed May 3, 2008]

BIBLIOGRAPHY

Ahmed, R., Oldstone, M. B., Palese, P. 2007. Protective immunity and susceptibility to infectious diseases: Lessons from the 1918 influenza pandemic. *Nature Immunology*. 8:1188–1193.

American Academy of Pediatrics. 1999. Combination vaccines for childhood immunization: Recommendations of the Advisory Committee on Immunization Practices. *Pediatrics*, 103:1064–1077.

American Academy of Pediatrics, Committee of Infectious Diseases. 1999. Poliomyelitis prevention: Revised recommendations for use of inactivated and live oral poliovirus vaccines. *Pediatrics*, 103:171–172.

American Academy of Pediatrics Committee on Infectious Diseases. 2007. Recommended immunization schedules for children and adolescents — United States, 2007. *Pediatrics*, 2007 Jan; 119(1), 207–208.

Anderson, C. 1991. Cholera epidemic traced to risk miscalculation. *Nature*, 354:255.

Angelini, R., Finarelli, A., Angelini, P., Po, C., Petropulacos, K., Macini, P., Fiorentini, C., Fortuna, C., Venturi, G., Romi, R., Majori, G., Nicoletti, L., Rezza, G., Cassone, A. An outbreak of chikungunya fever in the province of Ravenna, Italy. *EuroSurveillance Weekly*. 2007;12(9):E070906.1. http://www.eurosurveillance.org/ew/2007/070906.asp#1 [accessed October 3, 2007]

Ashmore, J., Addiman, S., Cordery, R., Maguire, H. 2007. Measles in north east and north central London, England: A situation report. *Eurosurveillance Weekly*, 12:E070920.2. http://www.eurosurveillance.org/ew/2007/070920.asp#2 [accessed October 3, 2007]

Brooks, G. E., Butel, J. S., Morse, S. A. 2004. *Jawetz, Melnick and Adelberg's Medical Microbiology*, 23rd ed. Stamford, CT: Appleton & Lange.

Centers for Disease Control. 1992. Update: International Task Force for Disease Eradication, 1990 and 1991. *Morbidity and Mortality Weekly Report*, 41:40–42.

Centers for Disease Control. 1993. Isolation of *Vibrio cholerae* O1 from oysters—Mobile Bay, 1991–1992. *Morbidity and Mortality Weekly Report*, 42:91–93.

Centers for Disease Control. 1993. Diphtheria outbreak—Russian Federation, 1990–1993. *Morbidity and Mortality Weekly Report*, 42:840–841, 847.

Centers for Disease Control. 1993. Resurgence of pertussis—United States, 1993. *Morbidity and Mortality Weekly Report*, 42:952–953, 959–960.

Centers for Disease Control. 1993. Update cholera—Western hemisphere, 1992. *Morbidity and Mortality Weekly Report*, 42:89–91.

Centers for Disease Control. 1994. Addressing emerging infectious disease threats: A prevention strategy for the United States. Executive summary. *Morbidity and Mortality Weekly Report*, 43(RR-5):1–18.

Centers for Disease Control. 1994. Rift Valley Fever—Egypt 1993. *Morbidity and Mortality Weekly Report*, 43:693, 699–700.

Centers for Disease Control. 1994. Rubella and congenital rubella syndrome—United States, January 1, 1991–May 7, 1994. *Morbidity and Mortality Weekly Report*, 43:397–401.

Centers for Disease Control. 1994. Update: Outbreak of Legionnaire's disease associated with a cruise ship, 1994. *Morbidity and Mortality Weekly Report*, 43:574–575.

Centers for Disease Control. 1996. The role of BCG vaccine in the prevention and control of tuberculosis in the United States: A joint statement by the Advisory Council for the Elimination of Tuberculosis and the Advisory Committee on Immunization Practices. *Morbidity and Mortality Weekly Report*, 45(RR-4):1–18.

Centers for Disease Control. 1996. Compendium of animal rabies control, 1996: National Association of State Public Health Veterinarians. *Morbidity and Mortality Weekly Report*, 45(RR-3):1–9.

Centers for Disease Control. 1997. Case definition for infectious conditions under public health surveillance. *Morbidity and Mortality Weekly Report*, 46(RR-10):1–55.

Centers for Disease Control. 1997. Tetanus surveillance—United States, 1991–1994. *Morbidity and Mortality Weekly Report*, 46(SS-2): 15–25.

Centers for Disease Control. 1998. Impact of the sequential IPV/OPV schedule on vaccination coverage — United States, 1997. *Morbidity and Mortality Weekly Report*, 47:1017–1019.

Centers for Disease Control. 1998. National, state and urban area vaccination coverage levels among children aged 19–35 months — United States, July 1996–June 1997. *Morbidity and Mortality Weekly Report*, 47:108–116.

Centers for Disease Control. 1998. Primary and secondary syphilis—United States, 1997. *Morbidity and Mortality Weekly Report*, 47:493–497.

Centers for Disease Control. 1998. Progress toward elimination of *Haemophilus influenzae* type b disease among infants and children in the United States, 1987–1997. *Morbidity and Mortality Weekly Report*, 47:993–998.

Centers for Disease Control. 1998. Recommendations and reports — Vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of measles: Recommendations of the Advisory Committee on Immunization Practices. *Morbidity and Mortality Weekly Report*, 47(RR-8):1–59.

Centers for Disease Control. 1998. Varicella related deaths among children — United States, 1997. *Morbidity and Mortality Weekly Report*, 47:365–368.

Centers for Disease Control. 1999. Progress toward global poliomyelitis eradication. *Morbidity and Mortality Weekly Report*, 48:416–421.

Centers for Disease Control. 1999. Ten great public health achievements — United States, 1900–1999. *Morbidity and Mortality Weekly Report*, 48:241–243.

Centers for Disease Control. 1999. Achievements in public health, 1900–1999. Impact of vaccines universally recommended for children — United States, 1990–1998. *Morbidity and Mortality Weekly Report*, 48:243–248.

Centers for Disease Control. 2003. Progress toward global eradication of dracunculiasis, January – June 2003. *Morbidity and Mortality Weekly Report*, 52:881–883.

Centers for Disease Control. 2004. 150th anniversary of John Snow and the pump handle. *Morbidity and Mortality Weekly Report*, 53:783.

Centers for Disease Control. 2004. Increases in fluoroquinolone-resistant *Neisseria gonorrhoeae* among men who have sex with men — United States, 2003, and revised recommendations for gonorrhea treatment. *Morbidity and Mortality Weekly Report*, 53:335–338.

Centers for Disease Control. 2005. Pertussis — United States, 2001–2003. *Morbidity and Mortality Weekly Report*, 54:1283–1286.

Centers for Disease Control. 2006. Effects of measles-control activities — African Region, 1999–2005. *Morbidity and Mortality Weekly Report*, 55:1017–1021.

Centers for Disease Control. 2006. Key facts about avian influenza (bird flu) and avian influenza A (H5N1) virus. *CDC Fact Sheet*, http://cdc.gov/flu/avian [accessed October 3, 2007]

Centers for Disease Control. 2006. Measles — United States, 2005. *Morbidity and Mortality Weekly Report*, 55:1348–1351.

Centers for Disease Control. 2006. Mumps epidemic — United Kingdom, 2004–2005. *Morbidity and Mortality Weekly Report*, 55:173–175.

Centers for Disease Control. 2006. Preliminary FoodNet data on the incidence of infection with pathogens transmitted commonly through food — 10 states, United States, 2005. *Morbidity and Mortality Weekly Report*, 55:392–395.

Centers for Disease Control. 2006. Preventing tetanus, diphtheria, and pertussis among adults: Use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP) and Recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for Use of Tdap Among Health-Care Personnel. 55(RR-17):1–33.

Centers for Disease Control. 2006. Recommended childhood and adolescent immunization schedule — United States, 2006. Harmonized childhood and adolescent immunization schedule. *Morbidity and Mortality Weekly Report*, 54:Q1–Q4.

Centers for Disease Control. 2006. Progress toward tuberculosis control and determinants of treatment outcomes — Kazakhstan, 2000–2002. *Morbidity and Mortality Weekly Report*, 55:11–15.

Centers for Disease Control. 2006. STD-prevention counseling practices and human papillomavirus opinions among clinicians with adolescent patients — United States, 2004. *Morbidity and Mortality Weekly Report*, 55:1117–1120.

Centers for Disease Control. 2006. Update: Influenza activity — United States and worldwide, May 21–September 9, 2006. *Morbidity and Mortality Weekly Report*, 55:1021–1023.

Centers for Disease Control. 2006. Vaccine preventable deaths and the global immunization vision and strategy, 2006–2015. *Morbidity and Mortality Weekly Report*, 55:511–515.

Centers for Disease Control. 2006. Primary and secondary syphilis — United States, 2003—2004. *Morbidity and Mortality Weekly Report*, 55:269–273.

Centers for Disease Control. 2007. National, state, and local area vaccination coverage among children aged 19–35 months — United States, 2006. *Morbidity and Mortality Weekly Report*, 31:56: 880–885.

Centers for Disease Control. 2007. Vaccination coverage among children in kindergarten — United States, 2006–07 school year. *Morbidity and Mortality Weekly Report*, 17:56:819–821.

Centers for Disease Control. 2007. West Nile virus activity — United States, 2006. *Morbidity and Mortality Weekly Report*, 56:556–559.

Centers for Disease Control. 2008. Updated recommendation from the Advisory Committee on Immunization Practices (ACIP) for use of 7-valent pneumococcal conjugate vaccine (PCV7) in children aged 24–59 months who are not completely vaccinated. *Morbidity and Mortality Weekly Report*, 57:343–344.

Centers for Disease Control. 2008. Measles — United States, January 1–April 25, 2008. *Morbidity and Mortality Weekly Report*, 57 (May 1, 2008 Early Release):1–4.

Cinatl, J. Jr, Michaelis, M., Doerr, H. W. 2007. The threat of avian influenza A (H5N1). Part I: epidemiologic concerns and virulence determinants. *Medical Microbiology, Immunology*, 196:181–190.

Diseases of Environmental and Zoonotic Origin Team, ECDC. 2007. Chikungunya in Italy: Actions in and implications for the European Union. *Eurosurveillance Weekly*, 12:E070906.2.

Editorial. 2007. *Helicobacter pylori*: Primary antimicrobial resistance and first-line treatment strategies. *Euro Surveillance Weekl*, 12(7) [Epub ahead of print].

Elderd, B. D., Dukic, V. M., Dwyer, G. 2006. Uncertainty in predictions of disease spread and public health responses to bioterrorism and emerging diseases. *Proceedings of the National Academy of Sciences*, 17;103:15693–15697.

Elliman, D. A., Bedford, H. E. 2007. MMR: Where are we now? *Archives of Diseases of Children*. 2007 Jul 11 [Epub ahead of print].

Gayer, M., Legros, D., Formenty, P., Connolly, M. A. 2007. Conflict and emerging infectious diseases. *Emerging Infectious Diseases*, http://www.cdc.gov/EID/content/13/11/1625.htm [accessed October 3, 2007]

Girou, E., et al. 2002. Efficacy of handrubbing with alcohol based solution versus standard handwashing with antiseptic soap: Randomised clinical trial. *British Medical Journal*, 325:36.

Goodman, R. A., Foster, K. L., Trowbridge, F. L., and Figuero, J. P. (eds.). 1998. Global disease elimination and eradication as public health strategies: Proceedings of a conference held in Atlanta, Georgia, USA, 23–25 February 1998. *Bulletin of the World Health Organization*, 76(Suppl 2):1–161.

Halstead, S. B. 1992. The 20th century pandemic: Need for surveillance and research. *World Health Statistics Quarterly*, 45:292–298.

Hargreaves, S. 2007. Infectious disease surveillance update. *Lancet Infectious Diseases*, (07)70154–8.

Hill, D. R., et al. 2006. Oral cholera vaccines: Use in clinical practice. *Lancet Infectious Diseases*, 6:361–673.

Humphreys, H. 2007. Control and prevention of healthcare-associated tuberculosis: The role of respiratory isolation and personal respiratory protection. *Journal of Hospital Infection*, 66:1–5.

Influenza Team (ECDC). 2007. Human influenza A/H5N1 ("pre-pandemic") vaccines: Informing policy development in Europe. *Eurosurveillance Weekly*, 12:E070920.3.

Klevens, R. M., et al. 2007. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Reports*, 122:160–166.

Ledrans, M., Quatresous, I., Renault, P., Pierre, V. Outbreak of chikungunya in the French Territories, 2007: Lessons learned. *Eurosurveillance Weekly*, 12:E070906.3. http://www.eurosurveillance.org/ew/2007/070906.asp#3 [accessed October 3, 2007]

Lee, G. M., Santoli, J. M., Hannan, C., Messonnier, M. L., Sabin, J. E., Rusinak, D., Gay, C., Lett, S. M., Lieu, T. A. 2007. Gaps in vaccine financing for underinsured children in the United States. *Journal of the American Medical Association*, 298:680–682.

Levine, O. S., et al. 2006. Pneumococcal vaccination in developing countries. *Lancet*, 367:1880–1882.

Lombard, M., et al. 2007. A brief history of vaccines and vaccination. *Review of Science and Technology*, 26:29–48.

Lopalco, P. L. 2007. Measuring the impact of PCV7 in the European Union: Why it is a priority. *Eurosurveillance Weekly*, 12:E070614.6.

Malfertheiner, P., Megraud, F., O'Morain, C., Bazzoli, F., El-Omar, E., Graham, D., et al. 2007. Current concepts in the management of *Helicobacter pylori* infection: The Maastricht III Consensus Report. *Gut*, 56:772–781.

Matsumoto, C., et al. 2000. Pandemic spread of an O3:K6 clone of *Vibrio parahaemolyticus* and emergence of related strains evidenced by arbitrarily primed PCR and toxRS sequence analyses. *Journal of Clinical Microbiology*, 38:578–585.

Meya, D. B., McAdam, K. P. 2006. The TB pandemic: An old problem seeking new solutions. *Journal of Internal Medicine*, 261:309–329.

Mulholland, E. K. 2006. Measles in the United States. *New England Journal of Medicine*, 355:440–443.

Muto, C. A., et al. 2003. SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of *Staphylococcus aureus* and enterococcus. *Infection Control and Hospital Epidemiology*, 24:362–386.

Peiris, J. S., de Jong, M. D., Guan, Y. 2007. Avian influenza virus (H5N1): A threat to human health. *Clinical Microbiological Review*, 20:243–267.

Peterson, Z. A., Kremer, M. 2007. What works in fighting diarrheal diseases in developing countries? A critical review. *Working Papers, Center for International Development at Harvard University*, Boston, MA. http://www.cid.harvard.edu/cidwp/pdf/140.pdf [accessed October 3, 2007]

Pittet, D. 2005. Considerations for a WHO European strategy on healthcare–associated infection, surveillance, and control. *Lancet Infectious Diseases*, 5:242–250.

Raviglione, M. C., Snider, D. E., Kochi, A. 1995. Global epidemiology of tuberculosis: Morbidity and mortality of a worldwide epidemic. *Journal of the American Medical Asociation*, 273:220–226.

Sinha, A., et al. 2007. Cost-effectiveness of pneumococcal conjugate vaccination in the prevention of child mortality: An international economic analysis. *Lancet*, 369:389–396.

Slutsker, L., et al. 1997. *Escherichia coli* O157:H7 diarrhoea in the United States: Clinical and epidemiologic features. *Annals of Internal Medicine*, 126:505–513.

Smith, K. F., Sax, D. F., Gaines, S. D., Guernier, V., Guégan, J. F. 2007. Globalization of human infectious disease. *Ecology*, 2007 Aug; 88(8), 1903–1910.

Sonnenberg, P., Crowcroft, N. S., White, J. M., Ramsay, M. E. 2007. The contribution of single antigen measles, mumps and rubella vaccines to immunity to these infections in England and Wales. *Archives of Diseases of Children*, 92:786–789.

Spanaki, A., Hajiioannou, J., Varkarakis, G., Antonakis, T., Kyrmizakis, D. E. 2007. Mumps epidemic among young British citizens on the island of Crete. *Infection*, 35(2):104–106.

Stern, A. M:, Markel, H. 2005. The history of vaccines and immunization: Familiar patterns, new challenges. *Health Affairs*, 24:611–621.

Stewart-Freedman, B., Kovalsky, N. 2007. An ongoing outbreak of measles linked to the United Kingdom in an ultra-orthodox Jewish community in Israel. *Eurosurveillance Weekly*, 12:E070920.1. http://www.eurosurveillance.org/ew/2007/070920.asp#1 [accessed September 28, 2007]

Suerbaum, S., Michetti, P. 2002. *Helicobacter pylori* infection. *New England Journal of Medicine*, 347:1175–1186.

Sullivan, T. 2004. *Helicobacter pylori* and the prevention of gastric cancer. *Canadian Journal of Gastroenterology*, 18:295–302.

Toungoussova, O. S., et al. 2006. Epidemic of tuberculosis in the former Soviet Union: Social and biological reasons. *Tuberculosis (Edinb.)*, 86(1):1–10.

Tulchinsky, T. H., et al. 1989. A ten-year experience in control of poliomyelitis through a combination of live and killed vaccines in two developing areas. *American Journal of Public Health*, 79:1648–1652.

Tulchinsky, T. H., et al. 1993. Measles control in developing and developed countries: The case for a two-dose policy. *Bulletin of the World Health Organization*, 71:93–103.

UNAIDS. 2006. *Report on the global AIDS epidemic: Executive summary*, Joint United Nations Proramme on HIV/AIDS, Geneva, Switzerland, 28 pp.

UNICEF. 2006. *The State of the World's Children*. New York: United Nations Children's Fund, Oxford Press.

U.S. Food and Drug Administration. 2007. FDA approves first U.S. vaccine for humans against the avian influenza virus H5N1. *FDA News*, 07(68):2 pp.

Watson, R. 2007. Chikungunya fever is transmitted locally in Europe for first time. *British Medical Journal*, 335:532–533.

Wells, C. D., et al. 2007. HIV infection and multidrug-resistant tuberculosis: The perfect storm. *Journal of Infectious Diseases*, 15(196): S86–107.

Wise, J. 2006. Demand for circumcision rises in a bid to prevent HIV. *Bulletin of the World Health Organization*, 84:509–511.

Wisner, B., Adams, J. 2002. *Environmental Health in Disasters and Emergencies: A Practical Guide*. Geneva: World Health Organization.

Wolfson, L. J., Strebel, P. M., Gacic-Dobo, M., Hoekstra, E. J., McFarland, J. W., Hersh, B. S. 2007. Has the 2005 measles mortality reduction goal been achieved? A natural history modelling study. *Lancet*, 20:369:165–166.

World Health Organization. 1990. *The Rational Use of Drugs in the Management of Acute Diarrhoea in Children*. Geneva: WHO.

World Health Orgaization. 1992. Update International Task Force for Disease Eradication 1991. *Morbidity and Mortality Weekly Report*, 41:40–42.

World Health Organization. 1996. Dracunculiasis: Global surveillance summary. *Weekly Epidemiological Record*, 71:141–148.

World Health Organization. 1996. Progress toward the elimination of leprosy as a public health problem. *Weekly Epidemiological Record*, 71:149–156.

World Health Organization. 1998. *Health for All in the Twenty-first Century*. EB101/8. Geneva: WHO.

World Health Organization. 1999. Integration of vitamin A supplementation with immunization. *Weekly Epidemiological Record*, 74:1–6.

World Health Organization. 1999. Rotavirus vaccines: WHO position paper. *Weekly Epidemiological Record*, 74:33–38.

World Health Organization. 2001. Global prevalence and incidence of selected curable sexually transmitted diseases: Overview and estimates. Geneva: World Health Organization.

World Health Organization. 2003. Treatment of tuberculosis: Guidelines for national programs. Geneva: World Health Organization; 2003 (WHO/CDS/TB/2003.313).

World Health Organization. 2005. Roll Back Malaria Programme. Global Strategic Plan Roll Back Malaria 2005-2015. Geneva, WHO. http://www.rollbackmalaria.org/forumV/docs/gsp_en.pdf [accessed May 4, 2008]

World Health Organization. 2006. Dracunculiasis eradication: Ministerial meeting 5 May 2006. *Weekly Epidemiological Record*, 24:239–224.

World Health Organization. 2007. Global tuberculosis control: Surveillance, planning, financing. WHO Report 2007. Geneva: World Health Organization. WHO/HNM/TB/2007.376.

World Health Organization. 2007. Meeting of the immunization strategic advisory group of experts, November 2006 — conclusions and recommendations. *Weekly Epidemiological Record*, 82:1–16.

World Health Organization. 2007. Meeting of the International Task Force for Disease Eradication, 11 January 2007. *Weekly Epidemiological Record*, 82:197–205.

World Health Organization. 2007. Pneumococcal vaccine for childhood — A position paper. *Weekly Epidemiological Record*, 82:93–104.

World Health Organization. 2007. Progress towards interrupting wild poliovirus transmission, January 2006–May 2007. *Weekly Epidemiological Record*, 82:245–260.

World Health Organization. 2007. Progress towards the 2005 international targets for tuberculosis control. *Weekly Epidemiological Record*, 82:169–180.

World Health Organization. 2007. Stop TB Partnership has provided treatment for 10 million people in 6 years. *Weekly Epidemiological Record*, 82:206–207.

World Health Organization. 2007. Dracunculiasis eradication: Certification of interruption of transmission. *Weekly Epidemiologic Record*, 82:161–163.

Xing, Z., Carters, T. J. 2007. Heterologous boost vaccines for bacillus Calmette-Guerin prime immunization against tuberculosis. *Expert Review of Vaccines*, 6:539–546.

Zuckerman, J. N., et al. 2007. The true burden and risk of cholera: Implications for prevention and control. *Lancet Infectious Diseases*, 7:521–530.