Epidemiology and Control: Principles, Practice and Programs

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1 Introduction: Infection and Disease

The epidemiology of infectious diseases is concerned with the circumstances under which both infection and disease occur in a population and the factors that influence their frequency, spread, and distribution. It is critical to distinguish between infection and disease because the factors that govern their occurrence may be different and because infection without disease is common with many viruses. Infection indicates the introduction and multiplication of a biological agent within a host, leading to an interaction often manifest as an immune response. It is determined largely by environmental factors that govern exposure to the agent and by both intrinsic susceptibility and personal behavior of the host. Disease represents the host response to infection when it is severe enough to evoke a recognizable pattern of clinical manifestations. The factors that influence the occurrence and severity of this response vary with the characteristics of virus involved, its portal of entry, and the dose or inoculum size; but the most important determinants for many common infections lie within the host. Of these, the age and general health at the time of infection, genetic background, and immune status of the host are the most crucial.

This chapter deals with the principles, observational methods, and control techniques applicable to viral infection and disease in general; these concepts and approaches are explored in greater detail in individual chapters concerned with specific viruses or groups of viruses. For broader and fuller presentations of the epidemiologic principles, see texts in Suggested Reading, and for widely accepted definitions, see Ref. [1].

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2 The Agent

This section addresses general properties of viruses that are important to an understanding of their epidemiology but not their basic genetic, chemical, or structural composition or details of their physiologic or multiplicative properties. Chapters of this book on specific viral infections provide some information on these topics. Other sources to be consulted include textbooks on basic virology, such as Fields Virology [2] and others, and books on the more general topic of microbiology and infectious diseases [3, 4].

Several intrinsic properties of all pathogens, including viruses, are of importance in the production of infection and disease; these properties can be quantified and permit comparisons among viruses. One property, *infectivity*, is ability to infect the preferred target cell in a standard assay, usually measured as the minimum number of infectious units or particles required. It may involve the capacity for attachment to, entry into, and multiplication within a variety of host cells. A second property, *pathogenicity*, is defined as the ability of an infectious agent to produce clinically significant disease. A third property, *virulence*, has been used synonymously with the previous two terms but more formally refers to the proportion of infections that produce serious disease, classically measured as a ratio of fatal cases to the total number of infections. A fourth property is what might be described as adaptability, a reflection of genetic responsiveness to external perturbations often determined by the type and organization of its nucleic acid. Over their long evolutionary history, most viruses have either gradually accumulated key mutations or even integrated entire host genes that alter their capacity to cause disease or permit them to evade or circumvent specific host mechanisms of resistance. The proper series of mutations may have enabled a virus to utilize an alternative biochemical pathway or conferred variable degrees of resistance to antiviral agents. Rapidly replicating RNA viruses like influenza, human immunodeficiency virus, and hepatitis C virus are more error (mutation) prone than many DNA viruses. More sophisticated mechanisms of evasive

R.A. Kaslow et al. (eds.), *Viral Infections of Humans*,
DOI 10.1007/978-1-4899-7448-8_1,

adaptation have been adopted by larger DNA viruses like the herpesviruses. One such mechanism utilized by human herpesvirus 8 is exemplified by the incorporation of several viral homologues of human genes (e.g., *IL6*, *IRF3*), which may mimic their human counterparts and/or usurp their function [5, 6]. All of these properties are factors that may influence not only the capacity to initiate infection and produce disease but also the transmissibility of the agent.

3 The Host

Characteristics of the host that influence the occurrence of both infection and disease are numerous and highly variable. Some host factors that alter resistance and susceptibility to infection are identical to those that modulate the development and natural history of disease, but many others affect only one or the other. Age, sex, and race are the most longstanding and obvious factors for both.

Most of the effect of age on resistance to infection either is attributable to the development of immunity over time or reflects the mode of transmission. Infants and young children are susceptible to a whole range of infections that confer lifelong immunity once acquired. Many viral infections that are now largely prevented wherever vaccines are available (e.g., measles, mumps, rubella, varicella, and rotavirus) and others like respiratory syncytial virus have historically caused major childhood morbidity and mortality. Acquisition of certain herpesviruses (herpes simplex virus, cytomegalovirus, and Epstein–Barr virus) begins in the perinatal period via congenital transmission followed by slow and steady increases until adolescence, most likely through relatively casual direct contact. Then occurrence accelerates somewhat for the next several decades during the period of more intimate oral or sexual contact before leveling off after middle age.

The severity of an acute infection and the course of chronic one infection may also differ by the age at acquisition. For reasons not well understood, hepatitis A in older children and adults can be much more clinically apparent than in younger children who are often asymptomatic. Similarly, poliovirus is much more likely to produce paralytic disease in older persons than in young children. The age at which an individual becomes infected with HIV-1 is a strong determinant of the natural history of that infection (see Ref. [7] and Chap. 43).

For most viral infections, especially those occurring principally in childhood, the two sexes appear approximately equally susceptible. In adolescents and adults, differential rates of acquisition by sex may be due to obvious differences in anatomy or in the mode of transmission, as in the case of human papilloma virus and HIV-1, respectively.

Differences in infection rate by race or ethnicity can be divided into those known or likely to have genetic or other biologic origins versus those most likely due to other factors that correlate closely with race. Genetic factors are discussed below. For the nongenetic explanations, race is usually a surrogate marker for some other often readily apparent factor. Geographic distribution is the most obvious reason for large racial differences. Viruses that have reservoirs or life cycles that involve nonhumans would be expected to occur only in regions of the world where the animal populations may coincide with humans of one particular racial group. Exposure may differ by race because of behavioral differences. New HIV-1 infections in young gay men in the United States have surged more in blacks because of their relatively exclusive exposure network (see Chap. 43). HIV-2 is heavily concentrated in individuals of West African and Portuguese ancestry because the virus probably originated and mainly spread in the former Portuguese colonies on the west coast of sub-Saharan Africa.

Other host biological and behavioral factors are known or likely to influence acquisition of viral infection: general nutritional status and specific micronutrient or vitamin deficiency, cigarette smoking, medication, use of alcohol and other non-medicinal substances, occupation, marital status, and sexual practices.

Many of the above-mentioned factors may not only predispose to or protect from infection but also modulate the nature, severity, or course of disease. Table 1.1 contains a list of the host factors implicated with varying degrees of certainty as modulators of occurrence, severity, pace, or duration of some viral diseases.

It is biologically based immunity that is the fundamental host characteristic governing not only acquisition but also, probably more profoundly than the other factors, the pathogenesis and evolution of infection. Indeed, the influences of age, sex, race, and some of those others reflect in part the accompanying biologic functions that vary with those characteristics. There are many examples in which these host factors are almost certainly operating as surrogates for immune

Table 1.1 Host factors that influence the occurrence, course, or severity of disease

1. Age at onset of infection
2. Sex
3. Race
4. Genetic factors controlling an enormous array of immune response elements
5. Preexisting level of specific or nonspecific immunity
6. Iatrogenic immunosuppression
7. Behavior and lifestyle: sexual practices, smoking, alcohol, and recreational drugs
8. Dual infection or superinfection with other agents
9. Preexisting chronic conditions and pregnancy
10. Nutritional status
11. Psychological status (e.g., motivation, emotional crises, attitudes toward illness) [8]

status. Age is prime example. Childhood respiratory and enteric viruses produce life-threatening disease in infants but little or no illness in adults who have developed natural immunity. Conversely, infections with hepatitis A and polio viruses are often asymptomatic in young children but may produce significant clinical hepatitis and paralytic poliomyelitis in older individuals. Aging adults develop increasingly severe infections as their immunity in general and specifically to previously encountered viruses wanes. Sex differences in disease expression are generally less obvious. Disease due to influenza virus is more or less equally common and severe in men and women in general, but pregnant women experience more serious illness [9].

Apparent racial disparities exist in rates of infection, disease frequency, or expression. Various sources of surveillance data suggest that persons of African ancestry in the United States have higher rates of influenza, HCV, HPV, and other viral infections, while those of Asian ancestry have higher rates of HBV infection. However, in each case these differences are readily attributable to geographic, socioeconomic, or behavioral influences on acquisition, as noted earlier, and race is simply a marker of some combination of those factors rather than signifying an underlying immunologic or other biologic basis for the difference. On the other hand, some racial or ethnic differences in the disease manifestations (severity or natural history) will undoubtedly prove to be due to underlying immunogenetic heterogeneity.

Immunity exists in a continuum ranging from lowest (i.e., complete susceptibility) to highest (i.e., complete resistance). Resistance is either intrinsic or induced, and it can be induced either naturally or artificially. The basis for natural resistance or immunity to viral infection is briefly discussed just below; the strategy and resources employed for inducing resistance by immunization are addressed later in this chapter.

Mediators of natural resistance include components of primary defense systems such as cilia, mucus, the integument, and other physical and chemical inhibitors. However, resistance is even more dependent on the principal organs involved in generating the immune response—spleen, bone marrow, lymph nodes, and other lymphoid tissue—the structures on which the highly complex cellular and humoral immune systems are founded. Multiple cellular arms of the immune system dedicated to defending against viral infection. They operate through dozens of known and as-yet-unknown interlocking pathways in which monocytes; macrophages; dendritic cells; a wide array of T-helper, suppressor, and regulatory cells along with B lymphocytes and plasma cells are all orchestrated to stimulate or respond to each other in a coherent and effective manner. They may do so by a variety of mechanisms. Communication and function may occur through direct cell–cell contact or binding between receptor–ligand pairs on cell surfaces. Alternatively or additionally, these and other specialized cells may secrete cytokines, chemokines, complement, peptides, or other immunoactive substances, for which their target cells carry surface or intracellular receptors. Thus, countless different cell types in elaborate interlocking pathways execute any of a variety of assigned functions—signaling, activating, inhibiting, attracting, killing, etc.

Humoral immunity is generated by a cascade of interactions among dendritic cells, T and B lymphocytes, and plasma cells culminating in the production of immunoglobulins that serve as antibodies to the virus that initiated the response. Once activated by a virus, the humoral immune system engages in sequential production of immunoglobulins of the IgM, IgG, and IgA classes in different proportions that bind to surface or intracellular antigenic components of the virus. This binding improves with avidity (tightness) and affinity (antigen specificity) that increase during the days or weeks following onset of infection. The antibodies, often in conjunction with complement or other proteins, may neutralize or kill the virus directly or recruit cells with cytotoxic capabilities into the vicinity to accomplish that task.

Both cellular and humoral systems demonstrate what are known as innate and adaptive responses. Certain effector cells and molecules preexist in the host before any pathogen is encountered. These relatively unvarying elements have been recognized as the "first responders" because they mediate intrinsic or innate functions that are automatically and uniformly invoked in the first hours and days after a viral infection or other foreign intrusion. Soon after the innate response is underway, the adaptive parts of the systems are activated. Dendritic and other cells use molecules on their surface to present antigenic fragments to effector T lymphocytes individually in a process exquisitely specific to the offending virus. This specificity is generated by the huge variation in the human leukocyte antigen (HLA) genes that encode those surface proteins used for microbial antigen presentation. These molecules not only activate helper and cytotoxic T lymphocytes but also interact with another set of cognate receptors on the surface of natural killer (NK) cells; these NK cell receptors are also encoded by highly complex multigenic systems such as the leukocyte receptor complex (LCR), the natural cytotoxicity receptor (NCR) family, and the killer lectin-like receptor (KLR) family. The antibody-mediated humoral response is likewise largely adaptive. As with cell-mediated antigen presentation and the cytotoxic systems, the organization of the genes encoding immunoglobulins are likewise programmed for genetically governed rearrangements to provide for maximum adaptability and specificity. Moreover, not only do most antibodies bind with specificity for a particular class of viruses or a single member of the class, they also undergo structural maturation over time to conform even more closely to the specific target antigen.

All of these processes depend primarily on differential expression of hundreds to thousands of genetic loci relatively directly involved in the immune response. Many of the simplest, often monogenic immunodeficiencies with Mendelian patterns of inheritance and the infectious diseases that complicate them have been well catalogued, although new examples continue to surface [10]. On the other hand, very little of the overall genetic contribution to more complex multigenic infectious traits have yet been elucidated, but research in this field is charging ahead. An example of very direct genetic mediation of resistance to viral infection is the remarkable protection against HIV-1 infection afforded by the deletion of a portion of the gene for the viral co-receptor (*CCR5*) in individuals of European ancestry, described further in Chap. 43. Other clear instances of genetic mediation are the increased susceptibility to norovirus infection among carriers of the O blood group antigen compared with carriers of A or B antigen [11] and the predisposition of children with polymorphisms in the Toll-like receptor 3 gene (*TLR3*) to herpes simplex viral encephalitis [12]. In the past two decades, the explosion of knowledge in immunology and genetics has paralleled the rapid advances in molecular and computational technology. A more detailed summary of the rapidly expanding knowledge of immune system function is beyond the scope of this overview. The reader is referred to textbooks and the most current reviews of specific subjects for more complete coverage [13–15].

4 The Environment

The external environment can exert its influences on the virus itself or its mode of spread or on the biological or behavioral aspects of the host response. Although viruses survive or die within defined ranges of such physical factors as temperature, humidity, and air currents, variability between viral groups is high. Chemicals may be used as antiseptics or microbicides to kill viruses prophylactically, and the list of pharmaceuticals now available for antiviral therapy has been growing rapidly (see Sect. 10). These environmental factors may enhance or diminish survival of viruses, but they probably have a greater impact on routes of transmission and on patterns of host behavior.

In addition to physical and chemical factors, biological variables play a role as well. For insect-borne agents like the equine encephalitis viruses, whose survival may depend on migration patterns of an avian host or on overwintering in a mammalian reservoir, the environment exerts an obvious role in restricting transmission of infection and occurrence of disease to those areas that have the proper temperature, humidity, vegetation, and other features necessary for the insects. For viruses potentially transmitted by water, such as hepatitis A virus and noroviruses, a warm environment with poor sanitation and fecal contamination clearly increases exposure and transmission efficiency.

Climate also alters the social behavior of the host. In settings where high temperatures promote not only contact of hosts with water through swimming or drinking but also viral replication, transmission of waterborne gastrointestinal diseases is increased in polluted areas. Warm weather also brings closer contact with insect vectors of arboviruses and with dogs and other animal sources of rabies. Conversely, in the cooler seasons, people collect indoors, where crowding promotes transmission of airborne and droplet-borne infections. Spread in indoor environments is amplified by relative concentration of military personnel in barracks, residents of assisted living facilities, and assembly and dispersal of students coinciding with the periodic openings and closings of educational institutions. Furthermore, the relatively hot and dry environment in many homes and commercial buildings may impair the protective mechanisms on mucous surfaces and promote entry and attachment of certain respiratory viruses.

In tropical settings, heavy monsoon rains bring groups indoors and closer together much as they do during winter in colder climates. The incidence of common upper respiratory diseases in college students was as high in the warm climate where the University of the Philippines is situated as in the intemperate winters at the University of Wisconsin [16]. Community studies in India [17], Trinidad [18], and Panama [19] have documented high morbidity from influenza and other respiratory diseases in tropical settings where people aggregate inside, as with heavy rainfall or school attendance.

Cultural as well as physical environment can contribute to the spread of infection, as exemplified by the patterns of spread of HIV infection among gay bathhouse patrons, injectable substance abusers in “shooting” galleries, women offering sexual favors in exchange for crack cocaine [20], and long-distance truck drivers patronizing commercial sex workers [21].

5 Agent, Host, and Environment Interaction

It is obviously the interplay of those three cardinal elements that dictates where, when, and in whom viral infection occurs. Their interaction further determines whether the infection produces disease, how soon it begins, how it manifests itself, how severe it becomes, and how long it lasts.

To initiate infection a virus must be in the appropriate structural and functional state, reflected in the intrinsic properties described above. It must also be present in a quantity sufficient to penetrate the target host. That quantity, the *inoculum*, is the amount of virus available to be transmitted; and the minimum size of a viral inoculum needed to initiate infection varies with infectivity,

a property discussed earlier, as well as with other features of those three cardinal elements. Upon introduction of the minimum inoculum and successful attachment to and penetration of its target cells, the infection is established. Then, again depending on various features of the agent, host, and environment, the virus elicits a response that may or may not manifest clinically.

The degree of response an agent can evoke in the host immune system is known as its immunogenic potential or *immunogenicity*. It commonly refers to the ability of the natural infection to confer protection against reinfection or significant disease upon reexposure. This protective ability has typically been measured as the quantity of antibody that neutralizes or incapacitates the virus, but viruses may generate antibodies that do not neutralize or protect. Many of the classic acute childhood infections (e.g., measles, mumps, rubella, chicken pox, and other exanthematous conditions) are not merely strongly immunogenic but also usually confer lifelong immunity. In contrast, other viruses can either readily alter their antigenic makeup like influenza and some flaviviruses or produce persistent chronic infection like herpesviruses; by a variety of mechanisms, they have ingeniously avoided generating highly neutralizing antibody. HIV-1 is the master of evasive and adaptive mechanisms that allow it both to evolve rapidly and to persist for years without stimulating antibodies that neutralize.

In the context of immunization, immunogenicity represents the extent to which a vaccine can provide the same or similar degree of protection achieved in the course of natural infection. Many of the regimens for vaccination against those highly immunogenic infections have succeeded in mimicking very high levels of neutralizing antibody if not lifelong protection. The more basic biologic characteristics of the agent and the host that determine immunogenicity are addressed in texts on virology and immunology (see Sect. 1).

6 Incubation and Latency Periods

The interval of time between the sufficient exposure and the appearance of the first symptoms in the human host is the intrinsic *incubation period*. Viruses transmitted by arthropods or other animals have their own (extrinsic) incubation periods that vary with both the response within the animal and the external environmental factors that affect the animal populations. However, here the reference is only to the intrinsic incubation period. The variation in this interval in different diseases is considerable (Fig. 1.1). Viruses that do not require distant spread but are able to produce disease through multiplication at the site of implantation, such as the respiratory tract, tend to have short incubation periods on the order of 2–5 days. Arthropod-borne viral infections like dengue and yellow fever may have onsets as early as 2–3 days after a mosquito bite [22], whereas inoculation by small mammals may lead to longer incubation periods [23]. Viruses that require hematogenous spread and involve distant target organs such as the skin or CNS have incubation periods of 2–3 weeks. Rabies virus, dependent on spread along nerves, has a long and variable incubation period ranging from 8 days to a year or more. Of course, transmission of the prion-associated kuru is exceptional with onset documented as long 34–56 years after exposure [24]. In some diseases (e.g., poliomyelitis, dengue, hepatitis, and infectious mononucleosis), early symptoms or even a rash may accompany the period of initial invasion or viremia. With these infections an early phase may not be clinically recognized or occurs before the patient seeks medical care.

Knowledge of incubation periods has many practical uses. Epidemiologically, the former helps define the period of infectiousness: a patient is not usually infectious until close to the time of the appearance of clinical symptoms. In epidemics, knowledge of the mean, minimum, and

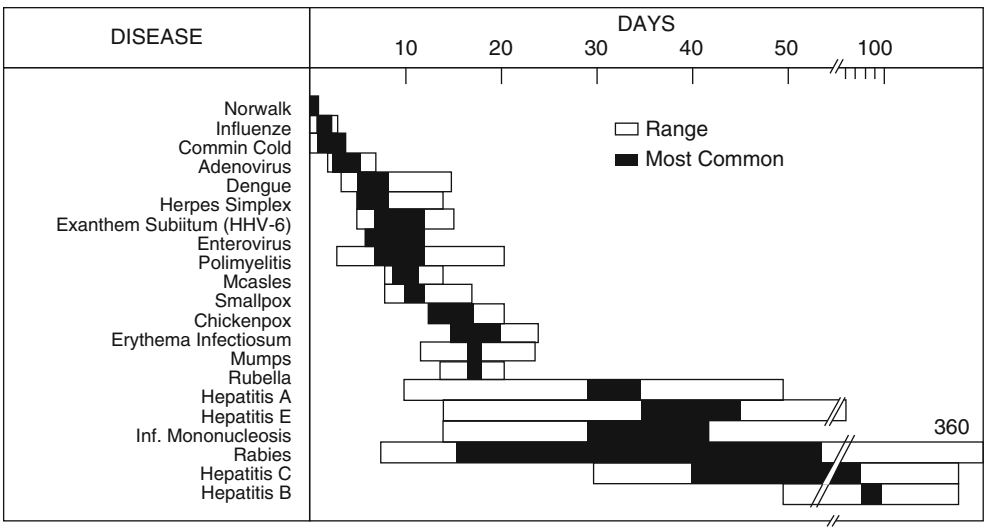


Fig. 1.1 Incubation periods in viral diseases (Based on data from Heymann [25]; Evans and Kaslow [210])

maximum intrinsic incubation periods can be used to identify the probable time of exposure to the index case or other source of infection. The duration of infectivity depends on the persistence of the virus and its exit into the environment. Clinically, the duration of the incubation period helps to identify the likelihood of viral exanthem after a known exposure or to differentiate hepatitis A from hepatitis B infections. For prophylaxis, it determines the feasibility of prevention of the clinical illness by immunoglobulin, as in hepatitis A and varicella zoster infections, rubella, and rabies, as well as the potential success of postexposure rabies vaccination.

In addition to the viruses that produce acute infections, there are delayed effects of certain common viruses in which the "incubation period" represents a true or apparent interval of "latency" lasting several to many years, during which there is little if any viral replication. Examples include the relationship of measles virus to subacute sclerosing panencephalitis, in which infection in infancy may be associated with involvement of the CNS some 5–10 years later [26]. Certain papovaviruses cause widespread inapparent infections in childhood. Rarely, reactivation occurs later in life in the form of progressive multifocal leukoencephalopathy. This phenomenon is seen in patients with Hodgkin's disease in association with depression of cell-mediated immunity and more recently in AIDS patients [27].

With HIV infection, a primary clinical response may occur within the first 2 months or so after infection in a substantial proportion of newly infected persons (see Sect. 7.1 and Chap. 43). During the subsequent clinically quiescent period, CD4 lymphocytes are destroyed at highly variable rates. Accordingly, clinical latency continues until immunosuppression is significant enough to permit new opportunistic pathogens to superinfect or long-latent agents to reactivate and produce clinical disease. The average time from initial HIV infection to that clinical event may be shorter or longer depending not only on the degree of viral control and immunosuppression under host genetic influence but also on the other cofactors required for any specific clinical AIDS outcome. For example, Kaposi's sarcoma tends to occur at a somewhat earlier stage of immunosuppression than cerebral atrophy with dementia or lymphoma for reasons presumably related to the unknown determinants of these conditions. Besides differences in the properties of the virus itself, such as the capacity to penetrate cells or induce syncytium formation in vitro, the route of transmission and host factors determine the rate of progression of HIV infection. The average AIDS-free interval is shorter for infants and children and for recipients of large volumes of blood products. The interval is longest among the youngest adults and then gradually shorter with increasing age [7]. There is also conclusive evidence for differential predisposition due to immunogenetic factors.

As with HIV infection, the latency period for different outcomes of HTLV-I varies. The interval between presumed infection via breast milk and onset of adult T-cell leukemia/lymphoma differs from the interval between presumed sexual transmission and onset of tropical spastic paraparesis or myelopathy. The concept of a latency period is also applicable to long-delayed virus-induced cancer as seen with an EBV-induced nasopharyngeal carcinoma KSHV-induced Kaposi sarcoma, HBV- and HCV-induced hepatocellular carcinoma, and HPV-induced cervical carcinoma (see Chaps. 34, 39, 40, 41, 44, and 45). In kuru, the latency period from exposure by ingestion of infected brain or other tissues or by absorption via abraded skin at a cannibalistic feast to the onset of disease can actually be as long as several decades (see Chap. 47) [24].

7 Patterns of Response

The response to viral infection varies along a biological gradient in terms of both the nature and the severity of the clinical syndrome produced. That variation is the product of the interaction of agent, host, and environment. The emphasis here is on the biological gradient as manifested in the human as a whole; qualitative and quantitative differences in responses that occur at the cellular and molecular levels are more properly the subject of basic virology and immunology texts.

7.1 The Biological Gradient

Response to a virus by an individual may range from completely asymptomatic to severe or fatal. The ratio of inapparent (or subclinical) to apparent (or clinical) responses varies from one virus to another; representative examples are shown in Table 1.2. The clinical response may be abrupt or more gradual, sometimes appearing long after the initial infection. It may be self-limited or arise from viral persistence or reactivation or both.

GBV-C infection increases with age but produces no known clinical illness [28]. Initial infection with BK and JC strains of polyomavirus, which show high prevalence and rates of acquisition of antibody in school children and adults [29, 30], is not known to affect them clinically. However, in immunocompromised patients (e.g., with AIDS, Hodgkin's disease, or renal transplantation), previously asymptomatic JC virus infection may evolve into progressive multifocal leukoencephalopathy[31]. Other primary or often reactivated infections are common in immunodeficient states; regardless of their clinical expression in normal hosts, most of the herpesviruses are more likely to cause mild to life-threatening complications.

Table 1.2 The gradient of subclinical/clinical ratio in selected viral infections (inapparent/apparent)

Virus	Clinical feature	Age at infection	Estimated subclinical/clinical ratio	Percentage of infection with clinical features
GBV-C	None known	Child to adult	∞	0
Poliomyelitis	Paralysis	Child	±1,000:1	0.1–1
Epstein–Barr	Heterophile-positive infectious mononucleosis	1–5	>100:1	1
		6–15	10–100:1	1–10
		16–25	2–3:1	35–50
Hepatitis A	Jaundice	<5	20:1	5
		5–9	11:1	10
		10–15	7:1	14
		Adult	2–3:1	35–50
Rubella	Rash	5–20	2:1	50
Influenza	Fever, cough	Young adult	1.5:1	60
Norovirus	Gastroenteritis	<2	1:5	60–90
HIV-1	Multiple	Any age	1:99	99
Measles	Rash, fever	5–20	1:99	99+
Rabies	CNS symptoms	Any age	0:100	100

A second group of viruses cause predominantly mild or asymptomatic infection when acquired in early childhood but symptomatic and sometimes severe clinical disease when infection is delayed. Examples of this are hepatitis A, poliovirus, and EBV.

At the other end of the spectrum are acute infections caused by agents like measles and rabies viruses or chronic infection with a virus like HIV-1 or the agents of spongiform encephalopathies, in which clinically recognized illness usually accompanies the infection but the course of infection may vary from days to decades. Rabies infection of man is the epitome of an infection from which death is virtually inevitable after characteristic symptoms develop.

The subclinical/clinical ratio for HIV-1 infection defies the more straightforward categorization possible for many other viral infections. A syndrome resembling mononucleosis with fever, fatigue, headache, lymph node swelling, joint and muscle aching, rash, sore throat, and other features occurs frequently in newly infected individuals. However, the proportion reported to have experienced this syndrome is higher or lower depending on the method of ascertainment (e.g., presentation at a sexually transmitted disease clinic, follow-up of cohort of initially uninfected homosexual men) and the clinical definition [32–34]. Likewise, the vast majority of HIV-1 infections follow a highly variable course—for a median of about 9 years in most studies of untreated individuals—free of the serious (AIDS-defining) illness; and on the average, HIV-2 infection progresses even more slowly. However, laboratory evidence usually indicates that immunologic deterioration is continuing at some rate even when the infection is clinically silent. The natural history of HIV infection and the factors that modulate it are addressed in detail in Chap. 43.

The biological gradient of many viral infections can be viewed as analogous to an iceberg in which clinically apparent illness represents only a small proportion of the response pattern and the usually larger amount represents unrecognized and inapparent infection. A similar analogy may exist at the cellular level. Figure 1.2 portrays these concepts, but Table 1.2 demonstrates that the precise shape of the iceberg for any given infection can vary considerably at the clinical level.

7.2 Clinical Syndromes: Manifestations, Etiologic Agents, and Frequencies

The tissue and organs targeted by human viruses can respond to infection in a limited number of ways; any of several viruses (or other causative agents) may trigger the same general response pattern. The clinician must often rely on epidemiologic and clinical features and simple laboratory tests in making a tentative etiologic diagnosis. This diagnostic reasoning may be based heavily on the known frequency of potential causative agents in the age group of the patient, the specific geographic or physical setting, the season, and their epidemic behavior. This section summarizes the major clinical syndromes produced by some of the more common human viruses. It includes (1) a very brief description of the clinical manifestations; (2) identification of major etiologic agents; (3) general frequency distributions by factors such as age and geography, not necessarily applicable at special times such as an epidemic or off-season or in settings like hospitals, nursing homes, and day-care facilities; and (4) selected other features relevant to the understanding of their occurrence in populations. For more detail, consult the chapter corresponding to the agent of interest or more specialized texts.

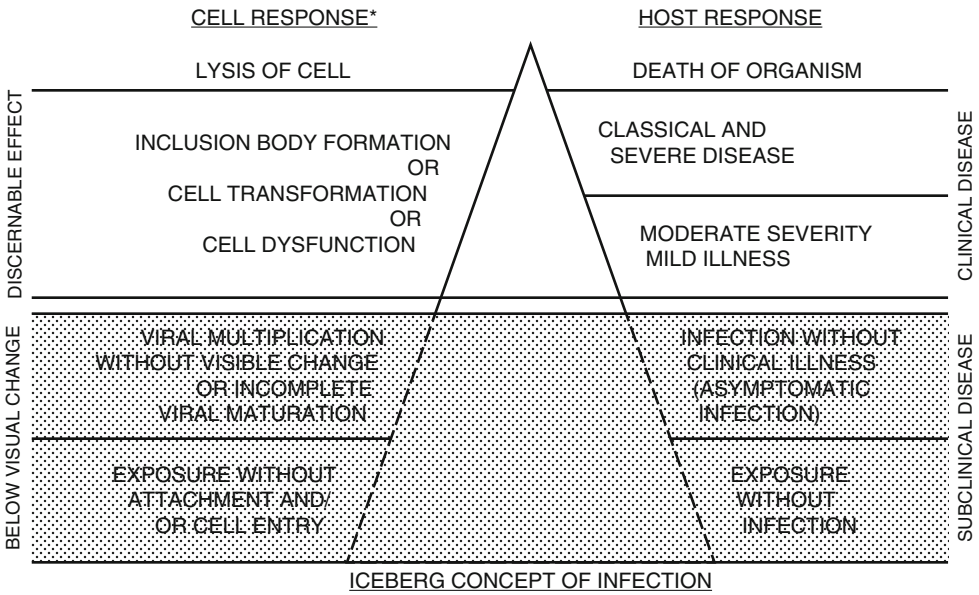


Fig. 1.2 "Iceberg" concept of infectious diseases at level of the cell and at level of the host. Within any cell population, varying patterns of cell response also occur. *Generic response [208] (Reproduced in Evans and Kaslow [210])

It is important to note that in recent years newer sample collection approaches, rapid immunologic assays, and highly sensitive molecular techniques have gradually supplemented and, in certain cases, supplanted the more traditional virologic and serologic tests, but they have come into use unevenly in different places (Chap. 2). Therefore, generalizations made in this discussion must be tempered by consideration of the methodology for sampling, detection, and identification that may have been used to generate the findings at different times in different settings.

7.2.1 Common Respiratory Tract Syndromes

Many viruses and viral groups can evoke symptoms and signs in the upper respiratory tract (e.g., eye, ear, nose, and throat symptoms; Viral infections of the lower respiratory tract trigger cough with little or no sputum production, shortness of breath, and changes in breath sounds on examination). Fever is less prominent than with bacterial or fungal infection.

Viral upper respiratory infection (URI) is extremely common in most temperate climates; it is the most frequent cause of absence from work or school in the United States [35]. A combination of rhinitis and pharyngitis (common cold) occurs most frequently in children under 5 years old, who may have multiple episodes in a single year. URIs are still frequent in older children, but incidence declines steadily through adulthood to greater than 60 years of age. Other manifestations of viral infection include sinusitis, which may be clinically or radiographically apparent in a very large proportion of those with viral URI [36].

Approximately nine of ten children under 2 years old have experienced an episode of otitis [37]. The usual viral etiologies are respiratory syncytial virus, parainfluenza (types 1–3), influenza (A and B), enterovirus, and rhinovirus [38]; however, the distribution of pathogens differs by age and location. Exposure to day care or a family member with a URI may be a predisposing factor.

Influenza virus is the leading cause of both upper and lower respiratory infections in middle-aged and older adults. Up to one-fifth of the entire US population may develop influenza in any particular season. Seasonal influenza typically lasts from November until March. However, in an atypical year, influenza activity may be present in summer and early autumn, as was true of H1N1 in 2009, when it overlapped with seasonal influenza, and of swine-associated H3N2v infection that occurred in 2012 in the setting of late summer county fairs [39].

Several viruses causing respiratory tract infection are relatively recent discoveries if not new to humans, and they are responsible for an appreciable proportion of viral respiratory tract infection (see Chaps. 10, 26, and 27). Human metapneumovirus can cause upper and lower respiratory tract infections (i.e., a cold, cough, bronchitis, pneumonia, and exacerbation of asthma) in people of all ages but more severe forms at the extremes of age and complicating immunosuppression. Coronaviruses, although known for years in animals and as the cause of more benign URI, came to attention dramatically during the large epidemic of severe acute respiratory syndrome (SARS) in 2003, and resurfaced again in the variant form producing Middle East Respiratory

Syndrome (MERS). Since then a succession of new human coronavirus strains has been associated with outbreaks of both upper and lower infections in different parts of the world. An even newer member of the parvovirus family, a bocavirus, has been at least presumptively linked with respiratory symptoms and otitis media [40].

Over the years, numerous investigators have tried to estimate the relative frequency of the different viral etiologies of clinical syndromes of acute respiratory diseases [40–48]. However, not surprisingly, the advent of newer more sensitive diagnostic techniques has made it increasingly clear that the distributions of viral pathogens vary greatly not only by age and season but also by geography and proximity to animal populations, previous human population experience, and other factors.

7.2.2 Gastroenteritis

This syndrome consists of nausea, vomiting, and/or diarrhea of varying severity, with relatively little fever or other features (e.g., significant abdominal pain or gross fecal blood) more typical of bacterial gastroenteritis. Worldwide, gastroenteritis causes serious morbidity and mortality, with the greatest toll in children under 5 years old, due to severe dehydration. In a study from the mid-1980s in the United States, diarrhea occurred in children under age 3 years in childcare at a rate of approximately three episodes per year [49]. Members of four families, rotaviruses, noroviruses, enteric adenoviruses, and astroviruses account for most of the disease caused by viruses, and each has epidemiologic characteristics that depend heavily on age and geography. Infections with these viruses tend to occur continually in children but only sporadically in adults. In the developed world, mortality is quite low although illness and hospitalization are more common.

Prior to the introduction of an effective vaccine, rotavirus infections were the leading cause of diarrheal illness in children under 2 years of age in the United States and many well-developed countries. The toll is still great in children under 5 years old in a number of places throughout the world, where it may account for as much as 30 % of mortality due to diarrheal disease [50]. As coverage with the vaccine expands, that picture is expected to change dramatically [51]. Caliciviruses and particularly the most notorious member of that family, norovirus, are now the leading cause of gastroenteritis among adults in the United States; these infections often occur in epidemic form as "winter vomiting disease" and are responsible for more than 90 % of outbreaks [52]. Facile interpersonal spread accounts for high secondary attack rates in family members and health-care personnel attending ill patients.

Viral gastroenteritis caused by adenoviruses and astroviruses has been studied more selectively, mostly in the United States. Specific serotypes of adenoviruses tend to cause disease in a year-round, endemic form, primarily in very young children. Up to 15 % of gastroenteritis in some settings may be due to astrovirus infection. Older children and adults are less affected. The infection is probably transmitted person to person, and it has caused infection in hospitalized and immunodeficient patients [11]. As many as another 10 % of cases in children may be caused by astroviruses, often in institutions like day-care centers and hospitals, where an even higher proportion of the transmitted enteric infections may be due to this agent [53, 54]. Elderly and immunocompromised patients appear to be at elevated risk [55, 56].

7.2.3 Common Central Nervous System Syndromes

Multiple viral agents are involved as causes of the syndromes of inflammation of the spinal cord (aseptic meningitis) and the brain (encephalitis) or a combination (meningoencephalitis). Comprehensive reviews of these infections can be found in Refs. [57–59]. The clinical features of these syndromes are quite variable, from mild headache and/or stiff neck with or without fever and subtle changes in cortical function (i.e., orientation, wakefulness, concentration, etc.) to more profound manifestations of spinal cord or brain dysfunction (including cranial nerve abnormalities; compromise of critical brain stem function; confusion, irritability, and poor feeding in very young children; and seizures). In younger children, long-term complications may include hydrocephalus, vision and hearing loss, weakness or paralysis, cranial nerve deficits, and learning and behavior problems.

The annual incidence of aseptic meningitis in the United States from all causes is approximately 11 in 100,000 persons, leading to 25,000–50,000 hospitalizations, mostly in children. However, many more mild and unconfirmed cases must go unreported. Again, the distribution of etiologic agents varies strongly with age, geography, and availability of vaccines.

The incidence of viral meningitis in infants may be as much as ten times that in older children. Worldwide, overall incidence is less easily estimated. Enteroviruses (echoviruses, coxsackieviruses, and others) are among the major causes in infants, and they may account for at least 80 % of cases in countries where vaccines against mumps, polio, and measles have significantly lowered the incidence of meningitis accompanying those conditions. On the other hand, in Asia, Japanese B encephalitis virus accounts for many thousands of meningitis cases each year and probably hundreds of thousands more that remain clinically inapparent.

Additional, less common causes include other flaviviruses (West Nile virus; see below), herpesviruses (VZV and others), lymphocytic choriomeningitis virus, other arboviruses (Eastern and Western equine encephalitis), and HIV-1. Because both enteroviral and arboviral infections show strong peaks in occurrence during the spring, summer, and early fall, the overall incidence in aseptic meningitis exhibits clear seasonality.

Encephalitis is less common than meningitis due to viral infection in the United States, with an annual incidence of about 20,000 cases or 3–8 in 100,000 persons. However, because many cases are not seen as part of an outbreak, an etiologic diagnosis requires a brain biopsy; therefore, only more severe and hospitalized cases are likely to receive such a specific diagnosis. HSV-1, the most frequent cause, is responsible for about 10 % of those cases. Arboviruses account for another 150 to several thousand cases, with variability according to the intensity of seasonal occurrence and striking peaks during sporadic epidemics. These have included Venezuelan equine encephalitis (1969–1971, several hundred cases), St. Louis encephalitis virus infection (1975, 3,000 cases), West Nile virus (encephalitis or meningitis, 2,800 cases in 2003 and 2,700 cases in 2012), and smaller numbers of La Crosse encephalitis and Western equine encephalitis cases [59]. In centers where concerted diagnostic effort is made, additional agents of sporadic cases of encephalitis and rarer central nervous system syndromes include other herpesviruses (EBV and VZV) and influenza A virus.

As with meningitis, accurate international estimates of the incidence of encephalitis are unreliable, but epidemic disease patterns similar to those in the United States occur throughout the world. For example, in a 1995 outbreak of Venezuelan equine encephalitis in Colombia and Venezuela, of the 75,000 humans estimated to have developed infection, neuroinvasive disease occurred in about 3,000, and 300 people died. Recently, henipaviruses in the paramyxovirus family have accounted for clusters of encephalitis and related neurologic disease in Australia along with Malaysia and Singapore (see Chap. 22).

7.2.4 Ocular Syndromes

Redness, watering, photophobia, feeling of irritation, and swelling of the membrane covering the eye (conjunctivitis) and the cornea (keratitis) are often severe symptoms epidemic keratoconjunctivitis (EKC) [60]. Outbreaks are commonly caused by very contagious human adenovirus infections. They are often nosocomial and have frequently occurred in such settings as the neonatal intensive care unit and ophthalmologic clinics, where contaminated contact lenses, eye drops, or instruments used for tonometry or slit-lamp examinations have been the modes of transmission (see Chap. 6).

Table 1.3 Viral causes of common exanthems

Type of rash	Examples[a]
Macular/papular	CMV, HHV-6, HBV, HIV
	Measles, atypical measles (vaccine)
	Rubella
	Echovirus
	Enterovirus 71
	Coxsackievirus
	Adenovirus
	Parvovirus B19 (erythema infectiosum)
Vesicular/pustular	Varicella zoster virus
	Smallpox
	Eczema herpeticum
	Eczema vaccinatum
	Coxsackievirus (esp. A16)
	Enterovirus 71
	Adenovirus [63]
	EBV [63]
	CMV [63]
Petechial or purpuric	Coxsackievirus (esp. A9)
	Echovirus, esp. 9
	EBV
	Atypical measles (vaccine)
	Parvovirus B19 [64]
Erythema multiforme	HSV-1 [65]
	Coxsackievirus A
	Echovirus
	Adenovirus
Others	Coxsackievirus A
	Echovirus
	HHV-8

[a]Examples of agents for each type of rash in table adapted from Cherry [66], except as noted by other citations [63–65]

7.2.5 Common Cutaneous Syndromes

Many viruses can produce one or more forms of eruption of the skin (exanthem). The most common acute viral infections involving the skin are listed in Table 1.3; many are classic exanthems of childhood including measles, rubella, varicella, erythema infectiosum or fifth disease caused by parvovirus B19, and roseola infantum (exanthem subitum) caused primarily by human herpesvirus type 6 (HHV-6) [61]. Rashes also occur in children or adults with coxsackieviruses and echoviruses [62], with certain adenoviruses (such as type 7), occasionally with EBV mononucleosis (often brought on by a reaction to ampicillin), and with other herpesviruses. HIV also causes a rash in a small proportion of newly infected patients. The distribution of these agents as causes of cutaneous conditions clearly varies by age, geography, vaccination status, and other host factors. The circumstances in which these many combinations of types of rash and agents are observed are not easily generalizable; the chapters on the individual agents should be consulted.

7.2.6 Hepatitis

Five principal agents are currently recognized as widespread causes of viral hepatitis: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis delta virus (HDV), and hepatitis E virus (HEV). However, viruses in a number of other families can produce hepatitis. In the parts of the world where yellow fever virus is prevalent, the syndrome is common. Less common agents are several herpesviruses (HSV-1, CMV, and EBV). All are associated with inflammation of the liver but with different severity, ranging from asymptomatic to acute mild liver tenderness and jaundice, often accompanied by malaise and anorexia, to fulminant hepatic failure in a fortunately small fraction of cases.

Two of the agents (HAV and HEV) produce more acute, usually mild to moderate self-limited illness, with milder illness in younger individuals. As enteric pathogens, they occur in geographic distributions that reflect socioeconomic conditions in those regions. Hepatitis A tends to occur sporadically in older individuals where immunity is high, often because poor sanitation permitted the virus to saturate the population at younger age. Conversely, epidemic HAV disease is more often seen in populations left susceptible as a result of better hygiene. In the United States and other countries where the vaccine against HAV is widely used, the decline in cases of hepatitis A has been striking. About 1.5 million cases occur annually worldwide. Hepatitis E is found worldwide, with different viral genotypes determining the disease distribution. Globally, genotypes 1 and 2 account for 70,000 deaths and 3.4 million cases often in outbreaks particularly in South and East Asia but in other developing countries as well, whereas genotype 3 occurs more sporadically in countries with better sanitation [67].

The three others (HBV, HCV, and HDV) have strikingly different clinical patterns. Both HBV and HCV may produce a range of symptoms including an acute syndrome much like that of HAV and HEV. However, a small proportion of HBV and the majority of HCV infections become chronic and often lifelong. In their chronic forms both infections may remain essentially quiescent for a lifetime or progress at quite variable rates to chronic inflammation and cirrhosis, with or without symptoms along the way, and both are responsible in some proportion for virus-induced hepatocellular carcinoma (see Chaps. 32, 33, and 34). Of the approximately two billion persons with HBV infection worldwide, 240 million have some degree of persistent infection of the liver, and 600,000 succumb to the sequelae [68]. The patterns of occurrence of these diseases are driven primarily by geographic and behavioral factors. Highly effective transmission by the parenteral, sexual, and perinatal routes accounts for the ubiquitous distribution of hepatitis B with particularly high prevalence in Asia. Until the introduction of vaccine, high prevalence in childbearing adults who transmitted the infection perinatally translated to high rates of chronic childhood infection and perpetuated the cycle. Throughout the world and in proportion to their representation in each population, hepatitis B has affected injection drug users (IDUs), recipients of contaminated blood products, those exposed to contaminated medical equipment, and men who have sex with men.

Because HCV is transmitted more by the parenteral and less by the sexual route, in the developed world, hepatitis C has been more confined to IDUs and others who have been exposed to contaminated blood and needles. Central Asia and East Asia along with North Africa and the Middle East have the highest prevalences of the HCV infection (>3.5 %) [69] as well as its incident sequelae hepatitis, cirrhosis, and cancer. Because of the highly variable absolute and relative prevalences of HBV and HCV infection and the other risk factors for those complications, it is difficult to estimate the incidence of HCV-induced cirrhosis or cancer or the risk attributable to HCV.

The delta virus (HDV) is an unusual partially defective RNA virus, closely dependent on the presence of HBV for its pathogenic expression if not for its multiplication. When HDV coinfects simultaneously with HBV, it may trigger an acute hepatitis syndrome but generally does not appreciably alter the course of disease. However, when HDV superinfects in a preexisting case of HBV infection, progression to cirrhosis is considerably more likely and often more rapid. The defective virus was first described in Europe, but it has been found at high prevalence in countries of sub-Saharan Africa, South America, and Asia where HBV is highly endemic, more often in parenterally infected blood product recipients or injection drug users and occasionally in men who have sex with men.

7.2.7 Perinatal Conditions

Infections of the fetus, neonate, and infant may be acquired from the mother in utero via placental transfer or during passage through the birth canal or from other individuals postpartum via nosocomial and other similar close contact. The major syndromes and their etiologic agents are tabulated below (Table 1.4). The specific clinical manifestations vary by agent and timing of infection relative to gestation. Vertically transmitted rubella, HSV-1/HSV-2, and cytomegalovirus infections have long been implicated as causes of especially severe congenital multiorgan anomalies [70]. Estimates of occurrence of perinatal infection vary according to location, personal hygienic and sexual activities, obstetric practices, utilization of vaccines, and other factors. Table 1.4 catalogues the major clinical consequences of the large number of agents responsible for perinatal infections.

The adverse outcomes of rubella during pregnancy, once numerically and clinically very important, have thankfully been virtually eliminated in the United States and other countries with effective vaccination programs. The fetal complications of the other vaccine-preventable diseases

Table 1.4 Effects of transplacental fetal infection

	Effect of infection on the fetus and newborn infant[a]				
Organism or disease	Prematurity	Intrauterine growth retardation and low birth weight	Developmental anomalies	Congenital disease	Persistent postnatal infection
Viruses					
Rubella	–	+	+	+	+
Cytomegalovirus	+	+	+	+	+
Herpes simplex	+	–	–	+	+
Varicella zoster	–	(+)	+	+	+
Mumps	–	–	–	(+)	–
Rubeola	+	–	–	+	–
Vaccinia	–	–	–	+	–
Smallpox	+	–	–	+	–
Coxsackie B	–	–	(+)	+	–
Echoviruses	–	–	–	–	–
Poliovirus	–	–	–	+	–
Influenza	–	–	–	–	–
Hepatitis B	+	–	–	+	+
Human immunodeficiency virus	(+)	(+)	(+)	(+)	+
Lymphocytic choriomeningitis virus	–	–	–	+	–
Parvovirus	–	–	–	(+)	–

Modified from Ref. [70]

[a]+, Evidence for effect; –, no evidence for effect; (+), association of effect with infection has been suggested and is under consideration

have also been drastically reduced. That has left CMV as the most common serious congenital disease due to viral infection in the United States [71]. It may infect more than 2 % of all pregnant women. About one-third of women with primary infection will transmit the virus to their newborn infants, but acquisition by mother and infant varies greatly with age, location, and socioeconomic conditions [72]. Both infection and serious sequelae are more common with primary than with recurrent infection. Congenital infection may be symptomatic in as many as 15 % of infected neonates [73]. Although these infections are usually benign, the virus can produce anomalies such as microencephalopathy, chorioretinitis, deafness, and mental retardation in a small proportion of those infected. Irreversible anomalies due to CMV infection occur in more than 5,000 children (0.1–0.2 %) each year.

Herpes simplex virus infections occur quite variably among pregnant women in different geographic, ethnic, and socioeconomic subpopulations. Infection in infants is almost always complicated by mucocutaneous (skin, eye, and mouth) lesions (75 %), encephalitis (57 %), pneumonia (18 %), or disseminated infection with combinations of the three (30 %). Prompt recognition is important because antiviral therapy is often effective in reducing morbidity. Estimates of incidence come from multiple sources. An early study from a single location found a frequency of 1 per 1,500 live births [74]. A more weighted population-based extrapolation from 2006 US hospitalization data yielded an incidence of 9.6 per 100,000 births [75].

The risk of perinatal HBV infection is primarily that of transmission of the virus from mothers who are chronically infected (i.e., HBsAg carriers). Although infection is not teratogenic and the reported impact on gestational age or birth weight must be quite infrequent [76], there are adverse consequences for the infected neonate who receives no immunoprophylaxis. About 5–8 % become hepatitis B surface antigen carriers during the first 6 months of life. Moreover, young adults infected in infancy are far more likely than those not infected until later to manifest not only persistent antigenemia but cirrhosis and, after an even longer latency period, hepatocellular carcinoma. Rates of infection in pregnant women show great geographic variation. Congenital and intrapartum HBV infection transmitted by maternal carriers has long been considerably more common in Asia and Africa than in Europe and the Western Hemisphere and has remained so. The pattern is changing in some places and will continue to do so wherever infant vaccination has been used routinely for more than two decades, and the earliest universally vaccinated birth cohorts are well into their childbearing years.

Untreated HIV-1 infection is transmitted from about 25–30 % infected mothers to their child/children. Adverse outcomes of pregnancy similar to those of perinatal herpesvirus and certain other infections have been reported with fetal and neonatal HIV-1 infection in some settings, but more recent systematic studies have not revealed clear causal associations [77, 78]. An accelerated course of infection and certain distinctive features (e.g., lymphocytic interstitial

pneumonitis) have been observed, potentially attributable to the unique attack on the immune system. Several regimens of antiretroviral agents alone or in combination have proved increasingly effective in interrupting perinatal transmission.

Parvovirus B19 has been repeatedly linked to anemia, neurological anomalies, hydrops fetalis, and fetal death (see Chap. 27). In an earlier prospective study of 156 mothers infected with this virus, 12 % delivered babies with some abnormality [79]. The investigators estimated the overall fetal risk to be 9 %, although higher in the second trimester, and the transplacental transmission rate to be 33 %. Adverse outcomes, particularly fetal loss and hydrops (a syndrome associated with destruction of red blood cells in utero), follow a proportion of the infections with this virus [79]. With a predilection for myocytes, it has also been implicated in myocarditis [80, 81].

7.2.8 Genital Tract Syndromes

Two families of viruses, HSV-1 and HSV-2, and several subtypes of HPV are common causes of conditions of the genital tract. Both HSV types can produce a spectrum of features ranging from no or minimal symptoms to an episode of fever; headache; myalgia; regional adenopathy; painful, tender blisters and ulceration on the epithelial surfaces of the genital organs and adjacent areas, including the anus and rectum; and dysuria. Small proportions of infected persons develop complications such as aseptic meningitis and proctitis (in men). Symptoms are more frequent and prominent with primary than with recurrent infection. Genital HSV infections are acquired through sexual contact, beginning with sexual debut and increasing through the earlier years of highest sexual activity in most areas of the world, where they are often the leading cause of genital ulcer disease. In recent years type 1 has matched or surpassed type 2 as a frequent cause of primary genital infection, particularly in younger persons. Infection with one of the two HSV types is extremely common; tens of millions of people in the United States have genital HSV infection [82]. Estimates from CDC indicated that in 2008, approximately 776,000 new HSV-2 infections occurred, with half being in persons under 25 years of age [83].

The two major manifestations of HPV infection are genital warts and squamous cell neoplasia. HPV types 6 and 11 and less frequently other types are responsible for genital warts (condyloma acuminata) on epithelial surfaces in the genital and anal area. The annual incidence of new cases of genital warts in the United States is about 360,000 persons [84]. Within the past decade, the cumulative incidence of genital warts in Scandinavian women up to age 45 years was about 10 % [85]. Among the unvaccinated group of women followed in a multinational trial of quadrivalent vaccine, approximately 1 % of the women developed warts each year [86]. HPV types 16 and 18 and less frequently other types cause a spectrum of cervical and vaginal cytological abnormalities that are largely benign but in diminishing proportions may progress to higher-grade neoplasia and culminate in invasive cervical carcinoma in a minority of women carrying those specific types. Annually worldwide, HPV causes about 500,000 cases of cervical cancer and ten million additional cases of premalignant neoplasia [87]. About 80 % of the cases and deaths occur in the developing world. The invasive cancer has a 50 % case fatality ratio. Analogous pathologic processes lead to anal and penile carcinoma, largely in men who have sex with men. The incidence rates of these cancers appear to be considerably lower than rates of cervical cancer in the same population [88].

7.2.9 Urinary Tract Syndromes

Acute hemorrhagic cystitis is the most prominent abnormality of the urinary tract caused by viruses. When the bladder inflammation is caused by the principal etiologic agents in children (adenoviruses, particularly serotypes 11 and 21 of subgroup B), hematuria may be recognized along with pain or burning, but the condition is often less symptomatic. Another possible viral etiology of a urinary tract syndrome (manifested as renal tubular damage) is BK virus, which, like other polyomavirus-related infections, tends to be pathogenic primarily in immunosuppressed patients.

7.2.10 Febrile Illness with Hemorrhage

Viral hemorrhagic fever may begin with a nonspecific prodrome of fever and chills, malaise, myalgia, headache, rash, flushing, and in some cases vomiting and diarrhea. These may rapidly progress to a multiorgan syndrome with petechial and more extensive bleeding but which is often less life threatening than vascular collapse with varying degrees of pulmonary edema, hypotension, shock, and renal failure. Variations of this syndrome are caused by a numerous and growing list of mostly vector-borne viruses in four families: arenaviruses, filoviruses, bunyaviruses, and flaviviruses (Table 1.5). Collectively, the viruses that produce this syndrome are found throughout the world although each individual agent is confined to the region where the principal arthropod vector or other animal reservoir lives. Certain of the diseases occur sporadically, for example, when a single individual has incidental contact with an infected animal. The occurrence of a cluster of cases is more ominous; because of the often fulminant illness and the unpredictable human-to-human propagation of cases, including nosocomial transmission, publicity about the event can have disproportional community impact. These phenomena have typified the ominously large outbreak of Ebola virus infection in West Africa. From time to time, one of these illnesses may present an immediate, major public health problem with hundreds of cases; there is, for example, concern about the potential for hemorrhagic dengue on a large scale in Southeast Asia.

Table 1.5 Families of viruses that may cause hemorrhagic fever

Arenaviridae	Bunyaviridae	Filoviridae	Flaviviridae
Argentine hemorrhagic fever	Crimean–Congo hemorrhagic fever (CCHF)	Ebola hemorrhagic fever	Dengue[a]
Bolivian hemorrhagic fever	Hantavirus pulmonary syndrome (HPS)	Marburg hemorrhagic fever	Kyasanur forest disease
Sabia-associated hemorrhagic fever	Hemorrhagic fever with renal syndrome (HFRS)		Omsk hemorrhagic fever
Venezuelan hemorrhagic fever	Rift Valley fever		Tick-borne encephalitis
Lassa fever			
Lymphocytic choriomeningitis (LCM)			

Adapted from [89]
[a]Dengue may occur in hemorrhagic form in certain circumstances (see Chap. 15)

Overall, the patterns of occurrence of these diseases are too variable to allow generalizations about their geographic distribution or the magnitude of the problem; they are addressed more individually in Chaps. 8, 9, 14, and 15.

8 Occurrence and Spread in Populations

In the broadest terms, viral propagation within an individual depends on properties such as the efficiency of spread from cell to cell, either by direct involvement of contiguous cells or by transport via body fluids to other susceptible cells; the number of cells infected; and the consequences of viral multiplication on the cell itself and on the organism as a whole. Further biochemical and physiologic details of these cellular processes are the subjects of more basic science texts. The next several sections are concerned with the occurrence and propagation of infection in populations, along with factors that influence those events.

Survival of human viruses depends on their long-term viability in human populations. Sustained viability, in turn, depends on the patterns of occurrence and propagation—within a host and between hosts. A virus must be capable of (1) infecting a host chronically without killing its cells; (2) infecting a host acutely and severely but escaping from the dying host cells as an intact, replicable entity in a manner that ensures its transport to a new susceptible host; or (3) infecting chronically or acutely but rapidly adapting to biological adversity such as exhaustion of susceptible hosts. Herpesviruses and other persistent viruses have evolved to establish durable relationships with their immunologically competent hosts. Arboviruses can destroy their hosts as long as the former can survive and replenish themselves in their nonhuman reservoirs and vectors. It is the viruses like influenza A and HIV, endowed with the greatest adaptability in the form of antigenic variation, that pose the greatest threat because they are not self-limited in their pathogenicity or in their dependence on favorable environmental conditions. Without its capacity for antigenic variation, influenza virus would, like measles or rubella virus, probably depend for survival on the temporal accumulation of new susceptibles. However, as noted earlier HIV has the powerful dual advantage of a retrovirus—capacity not only to vary its antigenic structure but also to establish latency for years.

8.1 Routes of Transmission

The major routes of transmission of selected viral infections are listed in Table 1.6. Viruses that have several alternate routes have an increased chance of infection. The sequence of events in transmission involves release of the virus from the cell, exit from the body, transport through the environment in a viable form, and appropriate entry into a susceptible host.

Some viruses are released from cells at the end of the cycle of multiplication. Others do not complete this cycle (incomplete viruses), and some are less effective at escaping (e.g., vaccinia). Many viruses are released from cells by budding, acquiring a lipoprotein coat or envelope as they go through the cell membrane; these include herpesviruses, togaviruses, myxoviruses, paramyxoviruses, and coronaviruses. Nonenveloped viruses not released by budding are the adenoviruses, parvoviruses, poxviruses, picornaviruses, and reoviruses. Some of these latter are released by cell lysis. Once released, viruses find their way to new hosts via one or more portals such as the respiratory tract (influenza, adenoviruses, RSV), skin (VZV and smallpox virus), blood (HIV, HTLV-I and HTLV-II, HBV, HCV, and arboviruses), gastrointestinal tract (enteroviruses, noroviruses, caliciviruses), genital tract (HIV, HTLV-I, HSV-2, and HPV), and placenta (rubella, HIV, CMV, HSV-1, and HSV-2). A more detailed presentation of these major routes of spread follows.

8.1.1 Respiratory

The respiratory route is probably the most important method of spread for most common viral diseases of man and is the least subject to effective environmental control.

Viruses transmitted principally by the airborne route include the agents of many classic childhood infections (e.g., rhinoviruses, measles, rubella, mumps, varicella, influenza, parainfluenza, respiratory syncytial virus). Of course, these

Table 1.6 Transmission of viral infections

Routes of exit	Mode of transmission	Example[a]	Factors	Routes of entry[b]
Respiratory tract	Bite	Rabies	Animal	Skin
	Saliva	EBV	Kissing	Mouth
			Prechewed food, infants	
		HBV	Dental work	
		HIV[c]	Sexual	
	Aerosol	Influenza, measles	Cough, sneeze	Respiratory
	Oropharynx to hands, surfaces	HSV, RSV, rhinovirus	Fomites	Oropharynx
Gastrointestinal tract	Stool to hands	Enteroviruses	Poor hygiene	Oropharynx
	Stool to water, milk food	HAV, rhinoviruses	Seafood, water, etc.	Mouth
		HAV, HEV		
	Thermometer	HAV	Nurses	Rectal
Skin	Air	Pox viruses	Vesicles	Respiratory
	Skin to skin	Molluscum contagiosum warts	Abrasions	Abraded skin
Blood	Mosquitos	Alphaviruses, flaviviruses	Extrinsic incubation period	Skin
	Ticks	Group B togaviruses	Transovarial transmission	Skin
	Transfusions of blood and its products	HIV, HBV, HCV, HTLV-I/HTLV-II, CMV, EBV	Carrier in plasma or lymphs	Skin
	Needles for injection	HIV, HBV, HDV	Drug addicts, tattooing	Skin
Urine	Rarely transmitted	CMV, measles, mumps, rubella	Unknown	Unknown
Genital	Cervix	HSV, CMV, HBV, HIV, HPV, rubella	Sexual, perinatal	Genital
	Semen	CMV, HBV, HIV	Heterosexual, homosexual	Genital, rectal
Placenta	Vertical to fetus	CMV, HBV, HIV, rubella	Infection in pregnancy	Blood
Eye	Tonometer	Adenovirus	Glaucoma test	Eye
Breast	Breastfeeding	CMV, HIV, HTLV-I	Maternal viremia	Mouth
Multiple organs Cornea, kidney	Transplant	Rabies, Creutzfeldt–Jakob disease	Surgery	

[a]*CMV* cytomegalovirus, *EBV* Epstein–Barr virus, *HAV* hepatitis A virus, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HDV* hepatitis delta virus, *HEV* hepatitis E virus, *HIV* human immunodeficiency virus, *HPV* human papilloma virus, *HTLV-I/HTLV-II* human T-lymphotropic virus type I/human T-lymphotropic virus type II, *RSV* respiratory syncytial virus

[b]Transmission does not always follow standard routes (Modified table from Evans and Kaslow [210] (Table 3), Springer has copyright)

[c]Likelihood of transmission by this route is controversial

are also transmitted among adults by this route as well. Others are transmitted by more direct contact with the nose or mouth or their mucosal secretions (e.g., EBV, HSV, and rabies virus).

Various other factors that affect airborne transmission of respiratory viruses include the intensity and method of propulsion of discharges from the mouth and nose, the size of the aerosol droplets created, and the resistance to desiccation. Much of the early work on the transmission of respiratory viruses was done by Knight and his group [90]. Direct transmission of infection occurs via personal contact such as kissing, touching of contaminated objects (hands, handkerchiefs, soft drink bottles), and direct impingement of large droplets produced by coughing or sneezing. These last two behaviors are regarded as personal contact because of the short range of the heavy droplets formed.

They also create aerosols varying in size up to >20 μm that permit transmission of infection at a distance. Dispersion of an aerosol depends on air currents and on particle size. In still air, a spherical particle with a unit density of 100-μm diameter requires 10 s to fall the height of the average room (3 m), and 40-μm particles require 1 min, 20-μm particles 4 min, and 10-μm particles 17 min. This means that particles under 10 μm have a relatively long circulation time in the ordinary room. Particles 6–10 μm or larger in diameter are more readily trapped upon direct impact in the nose and nasopharynx. Further into the airway, flow diminishes to the point where smaller particles 0.5–5 μm in diameter settle on the tracheal and bronchial walls by sedimentation, and particles of 0.5 μm in diameter or smaller can enter and deposit in the alveoli. As infectious secretions are discharged in large numbers by coughing or sneezing, the initially hygroscopic particles of 1.5-μm diameter lose moisture and shrink in ambient air and then regain their original dimensions from the saturated air as they are again deposited in the respiratory tract. Of course, virus particles in an aerosol may not necessarily settle at a level in the respiratory tree with the optimally susceptible cells for that agent.

High concentrations of particles of rhinovirus (and other viruses, including influenza) on fingers, hands, and hard surfaces indicate that infection via hands may be at least as important a route of spread as aerosols containing lower concentrations. This is supported by the continual inadvertent

contact of hands with the nose or eyes [91]. Therefore, frequent hand washing, using antiseptic-containing fluids, sprays, or gels, is recommended for controlling the spread of rhinoviruses, respiratory syncytial virus, and influenza and other viruses [92–95].

Aerosolization of certain viral agents may occur from suction devices and from catheters in intensive care units and from blood products in dialysis units. These include not only respiratory and intestinal agents but also agents such as HBV that circulate cell-free in the blood and cell-associated viruses such as CMV, EBV, HIV, and HTLV-1. Viruses aerosolized from urine or fecal material can be inhaled; hantavirus and arenaviruses are examples of agents that may be spread by aerosols created from soil containing the rodent urine or feces in which those viruses are excreted.

8.1.2 Enteric (Oral–Fecal)

Transmission by the oral–fecal route via the gastrointestinal tract as the portal of entry is probably the second most frequent means of spread of common viral infections.

The major enteric viruses are enteroviruses, rotaviruses, and calici-, polio-, echo-, and coxsackieviruses, along with HAV and HEV. Adenoviruses and reoviruses also multiply in and shed from the intestinal tract, but this route of transmission is not usually of epidemiologic importance. Despite their name, although enteroviruses multiply in cells lining the gastrointestinal tract, they rarely produce local disease there; they rather target the central nervous system and skin and produce their major symptoms and pathology in those organs. Likewise, hepatitis A and E viruses attack the liver, not enteric mucosal cells.

Viruses can directly infect susceptible cells of the oropharynx, but to induce intestinal infection, virus-containing material must be swallowed, successfully resist the hydrochloric acid in the stomach and the bile acids in the duodenum, and access susceptible cells in the intestine. Viruses with envelopes do not normally survive exposure to these acids, salts, and enzymes in the gut.

Agents excreted via the gastrointestinal tract must successfully infect other susceptible persons via fecally contaminated hands, food, water, milk, thermometers, insects, or other vehicles. Both HAV and HEV are stable viruses in water and, when present in sufficient dosage, may not be inactivated by ordinary levels of chlorine. Outbreaks of viral hepatitis have occurred from sewage-contaminated water, as in the huge outbreaks in New Delhi, India, in 1955 [96], and subsequently often due to HEV and in less dramatic attacks elsewhere. Furthermore, HAV, at least, can persist over long periods in oysters and clams obtained from fecally contaminated waters. Milk and water have also served as vehicles of transmission of other viral agents: caliciviruses and poliomyelitis viruses. This is especially hazardous because these foods are so often eaten without having been cooked. Hepatitis viruses and the enteroviruses also flourish in certain institutional settings (mental hospitals, institutions for retarded children, some prisons) and in countries where personal hygiene is lacking or difficult to practice or where poor environmental control is present.

For viruses spread by enteric routes, environmental control is much more effective than for those transmitted by the respiratory route. Thus, good personal hygiene, especially washing of hands after defecation, proper cleanliness and cooking of food, pasteurization of milk, good waste disposal, and purification of drinking water supplies have all proved to be effective preventive measures. On the other hand, some enteroviruses may also multiply in the respiratory tract and be transmitted by the respiratory route; therefore, this alternate pathway is of epidemiologic importance even in the face of good personal and environmental hygiene.

8.1.3 Direct Cutaneous Contact

Direct penetration of intact skin is a less common route of viral entry, and when it occurs, the viruses are usually carried in fluid or some other vehicle. Human papillomaviruses, the agents causing warts, enter through abraded skin and anogenital epithelium; prions, the agents of kuru, may also gain access that way. With rabies, viral penetration of the skin invariably involves an animal bite or some other source of contaminated biological fluid.

The skin serves as a portal of exit for those few viruses that produce skin vesicles or pox lesions that release infectious particles on rupture. These include herpes simplex, smallpox, varicella zoster, and vaccinia viruses. The viruses of certain maculopapular exanthems may also be present in the skin, as in rubella, but this does not seem to be an important avenue of escape, since vesicles are not formed and skin involvement occurs late in the disease, when the virus may be bound by antibody; indeed, the antigen–antibody complex may be responsible for the rash itself.

8.1.4 Sexual

The genital tract serves as a portal of both entry and exit for viruses that infect the genital tissues themselves and more remote target organs. It is also the source of intrapartum infection as the fetus passes through the birth canal. Herpes simplex types 1 and 2 cause ulcerative lesions of the anal and genital mucosa and the surrounding skin. Sexual transmission of these viruses can produce oropharyngeal lesions as well. These and other viruses (most frequently, CMV, HIV, HBV, and HPV) can also be transmitted to their target cells in the anogenital epithelial layer (HPV), in nearby subepithelial lymphoid system (HIV and CMV), or in remote hepatic tissues (HBV). Receptive anal intercourse is a particularly important method of spread of these infections. Three of these four viruses (CMV, HIV, and HBV) along with rubella virus are present in cervicovaginal secretions and can infect

infants perinatally (see Sect. 8.1.5). Finally certain types of HPV, principally 16 and 18, cause a substantial proportion of cervical infection leading to a spectrum of mucosal abnormalities including cervical cancer.

CMV, HBV, and HIV are present in the semen and/or female genital secretions and can be transmitted during either heterosexual or homosexual intercourse [97–101]. Long-term asymptomatic cervical or semen carrier states exist and make recognition and control difficult.

The presence of other genital infections has been shown in repeated studies to predispose to transmission of HIV-1 by the HIV-1-infected partner and acquisition of HIV-1 by the susceptible partner. Most epidemiologic data indicate that the ulcerative lesions of syphilis, chancroid, and HSV-2 infection mechanically facilitate penetration of the epithelial barriers of the genital tract by HIV [102, 103]. However, suggestions of predisposition by non-ulcerative infections like gonorrhea, chlamydiasis, trichomoniasis, and bacterial vaginosis are consistent with an alternative to enhanced epithelial penetration, namely, recruitment and activation of macrophages and other inflammatory cells responsive to the mucosal breach (see Chap. 43).

8.1.5 Intrauterine and Intrapartum

Viruses may infect the fetus either by direct contact via the birth canal or by hematogenous spread via the placenta to the fetus within the uterus. Herpes simplex virus and CMV infections can initiate intrauterine infection by more direct local contact, whereas CMV, hepatitis B, rubella, varicella, and HIV all infect the placenta by the hematogenous route. CMV is the most common congenital infection, whereas congenital rubella has sharply declined wherever vaccination has become routine. Acquisition of EBV or HBV in the early postnatal period is associated with persistence of infection and substantially increased risk of subsequent cancer (see Chaps. 32, 34, 40 and 41).

8.1.6 Blood-Borne

Direct inoculation of viruses into the blood requires some object sharp enough to penetrate the skin and the wall of a blood vessel. That can happen naturally through the bite of an arthropod vector (see Sect. 8.1.7) or iatrogenically through an injection, either with an inadvertently contaminated needle (e.g., by an injection drug user or in medical practice) or for administration of medicinal blood products (e.g., a transfusion). The agents best known for transmission by this route include hepatitis viruses (HBV, HCV, and HDV), retroviruses (HIV and HTLV), and herpesviruses (EBV, CMV). The mechanism of transmission for each of these viruses is similarly straightforward, with the likelihood of infection dependent on a combination of the intrinsic viral properties described above (Sect. 2), the delivery mechanics, and the dose or the size of the inoculum delivered.

8.1.7 Vector-Borne: Insects and Mammals

Humans may be primary or incidental hosts for numerous vector-borne viral infections. They may be transmitted through direct injection by mosquitos, ticks, flies, and other arthropods; they may also be spread directly through saliva during the bite of larger mammal; or they may be spread more indirectly through aerosolization of urine from a rodent. For some viruses, their life cycle involves multiplication in their vector. In many arboviral infections, virus acquired from the human or animal host during viremia requires a period of multiplication in the vector before it is infectious. Examples of this include the transmission of yellow fever virus by *Aedes aegypti* mosquitos and of the seasonally epidemic St. Louis, California, and equine encephalitis viruses. The vector life cycles can be complex, including overwinter survival with transovarian or sexual transmission within mosquito populations.

A range of mammals (dogs, bats, raccoons, skunks, foxes, and others) carry rabies virus in their tissues and bodily fluids including saliva. They can transmit to a human during a bite, with the likelihood of transmission varying according to several factors: the mammalian species, the level of viremia, the duration of its infection, the nature and location of the bite, and others. Bats may also transmit henipaviruses and coronaviruses. Rodent species can also carry and transmit viruses in their urine or feces. Examples of rodent transmission include hantaviruses and Lassa fever virus. The viruses transmitted by vectors can vary greatly in their host range from a fairly high degree of species specificity (as with dengue in *Aedes aegypti* or Lassa fever virus in one or possibly more closely related rat species) to a much broader range (as with rabies in a number of different mammalian families).

Another kind of transmission by a vector is simply mechanical, involving adherence of material containing virus to an insect and transportation from one host to another. This type requires neither incubation time in the insect vector nor any specificity for either the arthropod host or the virus. Enteric viruses like polio and possibly hepatitis viruses may be carried in this way.

8.1.8 Urinary

Interestingly, although viruses such as CMV and measles are excreted in the urine, this portal of exit has not been established as being of epidemiologic or clinical importance. Considering the wide variety of viruses that can multiply in human kidney tissue cultures in vitro and the likely role they play in immune complex nephritis, it seems surprising that renal infections with these viruses are not observed more frequently in humans.

8.1.9 Nosocomial

The unique populations and physical circumstances found in hospitals and other health-care facilities lead to the

transmission of many viral infections by several of the foregoing routes. The more than two-dozen viruses that have been documented as being nosocomially transmitted include many viruses that affect the respiratory tract as well as those transmitted through the respiratory tract to other organs and cells (e.g., CMV, HSV-1, HSV-6, and VZV) [104], hepatitis viruses (including HAV, HBV, and HCV) [105], enteric viruses (mainly rotavirus [106] and caliciviruses [107]), the viruses of several exanthems (rubella and measles) [108], and picornaviruses [106, 109–111].

Respiratory Route

Respiratory tract infections spread by droplets or droplet nuclei like influenza may disseminate naturally through both the relatively vulnerable patients and the personnel in close proximity to each other. Nosocomial respiratory syncytial virus (RSV) infection in patients and staff has been a major concern in the pediatric nursery, intensive care wards, or other population groups [92] at high risk due to crowding and often an immature immune system. Outbreaks among adults and elderly patients in health-care facilities have also been reported, with influenza being a major concern [112–115]. In these settings, infections, diseases, and outbreaks of CMV, HSV, VZV, enteroviruses, myxoviruses, metapneumoviruses, and parainfluenza viruses have also occurred [116–118].

Although viruses may also theoretically be transferred from one patient to another by contaminated ventilating equipment, with the exception of occasional reports about herpesviruses (CMV and HSV-1) [119, 120], this type of nosocomial transmission has not been recognized as an important one. Lack of concerted effort to detect viruses rather than their actual absence may explain the dearth of information about this phenomenon.

Enteric Route

As noted above, enteric viral infections are very common in acute and long-term health-care settings, and outbreaks (mainly due to rotavirus [106] and caliciviruses [121]) can involve large numbers of patients. The circumstances in which they are transmitted within health-care facilities do not differ greatly from those operating outside them (Sect. 8.1.2), although they appear to have a tendency to attack immunocompromised patients.

Direct Contact with Biologic Tissue and Fluids

Transmission of cutaneous and mucosal viral infections in health-care settings by direct contact is not especially common (VZV, HPV, HSV). Although viruses naturally transmitted through the skin following bites (rabies, in particular) rarely propagate that way in hospital settings, contact by personnel with tissue, saliva, and other secretions from transplant patients infected with rabies virus has led to serious consequences [122]. Corneal transplant has also been associated with transmission of the slow (Creutzfeldt–Jakob) virus [123]. These incidents have prompted the transplantation community to adopt exacting protocols for excluding organs and tissue that may be infected with potentially harmful viruses. Lassa fever, Ebola, and Marburg viruses have often been transmitted as nosocomial infections [124]. Lassa fever, in particular, has infected patients and staff, especially in the obstetrical wards via infected placentas.

Blood-Borne Route

Blood transfusion has long been a potential source of viral infection, and with each significant pathogen discovered to be transmissible by transfusion (HBV, HIV-1/HIV-2, HCV, HTLV-I/HTLV-II, and West Nile virus), the US Food and Drug Administration has orchestrated the development and implementation of universal donor screening [125]. Other viruses that are capable of transmission by blood products (e.g., CMV, EBV, parvovirus B19) appear to be relatively harmless and/or ubiquitous enough that screening is not deemed necessary.

Of major concern for patients is accidental exposure during procedures where there is direct contact with a potentially contaminated tissue (e.g., transplantation) or instrument (e.g., needle, dental or dialysis equipment, or endoscope). In regions of the world with adequate resources and training, universal blood precautions and the use of safety measures for disposing or auto-inactivating contaminated needles have largely but not entirely [126] eliminated percutaneous transmission of HBV, HCV, HIV, and other viruses by needlestick injuries. During the first 20 years of the HIV-1 epidemic in the United States, 57 cases of infection were due to occupational injury in health-care personnel [127]. From 1999 to 2012, no further cases had been documented. The Centers for Disease Control (CDC) continues to collect data and inform personnel about those risks [128, 129].

8.2 Measures of Occurrence

Incidence is the number of new events (e.g., instances of infection or cases of disease) occurring in some time interval. Generally, the *incidence rate* is the number of new events divided by the number of people at risk. The incidence rate may be expressed more specifically as the number of events per unit of population per unit of time or as the number of events in a fixed total population during a fixed total time period. The latter is considered a cumulative incidence but is often called an "attack rate" in an epidemic setting, where the total time period under consideration is established by the circumstances.

In the public health context, incidence may refer to new infections or new cases of disease. In the past, *incident*

infection was usually documented by isolation or pathologic visualization of newly acquired virus or by an assay for seroconversion—the appearance of new specific antibody or a defined increase in the titer or concentration of preexisting antibody; occasionally, new infection would be recognized by a change in the concentration of a specific biomarker like an enzyme. In the current molecular era, a variety of techniques for detecting viral nucleic acid are being used to establish newly acquired infection (see Chap. 2). In calculating an infection incidence rate, the denominator would ideally consist of all individuals in a population considered to be both exposed to the agent and susceptible (i.e., lack antibody or other evidence of prior infection).

Incident disease has always meant the presence of clinical manifestations—some combination of self-reported symptoms, objective physical signs, and positive results of specific diagnostic tests; and the disease incidence rate, is based on all individuals in a population whether or not they are infected.

Mortality can be thought of as the incidence of death. In calculating mortality, because the number with infection is seldom known, the total population is customarily used as the denominator, even though that rate generally underestimates the actual rate of death due to a specific viral infection. The case fatality ratio, another measure of the deadliness of an infection, is the proportion of all persons with cases who have died.

In public health practice, the populations at risk or infected can only be estimated with variable degrees of accuracy depending on the circumstances. Evidence of prior infection is often not available. Commonly, the best estimate possible is simply the total population present during a particular time interval within the geographic area or physical space (e.g., hospital) encompassed by the detection or reporting system. Public health agencies generally tabulate statistics for infection or disease in the form of annual rates.

Prevalence is the number of persons with infection or cases of disease existing at a designated time or in a time interval. The *prevalence rate* is the number of such cases divided by the population at risk. The time period involved may be a given instant of time (point prevalence) or a fixed period such as a year (period prevalence). The term *period prevalence* thereby incorporates both the number of new (incident) cases and the duration of illness (number of old cases persisting from the previous reporting period). It is used most commonly for chronic diseases.

Prevalence of infection is usually measured by a test for the presence of a substance (e.g., antibody, antigen, fragment of nucleic acid, or other component) in biological fluid or tissue samples from a given population at the time of their collection. In calculating a prevalence, the denominator consists of persons whose samples were tested. For viral infections, the prevalence of antibody (i.e., seroprevalence) represents the cumulative rate of infection with the agent over recent and some years past depending on the persistence of the antibody. For neutralizing or other long-lasting antibody, it reflects the cumulative or lifetime experience with that agent. If the antibody measured is present only transiently, as is often true of immunoglobulin M (IgM) antibody, then its prevalence indicates infection acquired within a recent period and may even approximate incidence. As with antibody, the detection of nucleic acid could signify either recent or more persistent infection, depending on the natural history of the infection. In calculating a viral disease prevalence, the denominator is usually all individuals in the total population.

It should be clear that the number of new (incident) cases and the number of existing (prevalent) cases are related to each other. More specifically, the prevalence of infection or disease is determined by the duration of incident cases: the longer the duration of an incident condition, the higher the number of prevalent cases of that condition. That proportionality can be represented as prevalence = incidence × duration. More strictly speaking, the term in the equation should be average duration, which may vary considerably for more chronic infections. Two corollaries of this relationship are that the prevalence of acute self-limiting illnesses of short duration would closely mirror the incidence, and the more variable the duration of the condition, the less reliable the relationship in a particular population may be.

8.3 Patterns of Occurrence

Infections at the population level do not happen randomly; they occur in patterns, with different characteristics and in different magnitudes.

8.3.1 Secular, Periodic, and Seasonal Trends

Secular trends in occurrence with no obvious periodicity have been observed over longer intervals than a single year. Numbers may rise or fall depending on natural factors. Short- or long-lived climate changes can alter the balance of vector and host populations, leading to significant increases or decreases in incident arboviral infections. Local populations experience gradually declining rates of a particular strain of respiratory virus as population-level immunity develops following repeated exposures.

Other factors, natural or human in origin, may produce periodic fluctuations that are not strictly seasonal because they do not recur each year at the same time. In the absence of high levels of vaccination, herd immunity to a disease like measles may produce periodic but not strictly seasonal waves of new cases every 2–4 years depending on how fast new susceptibles are introduced into a population (see Sect. 8.3.2). Human migration may account for periodicity

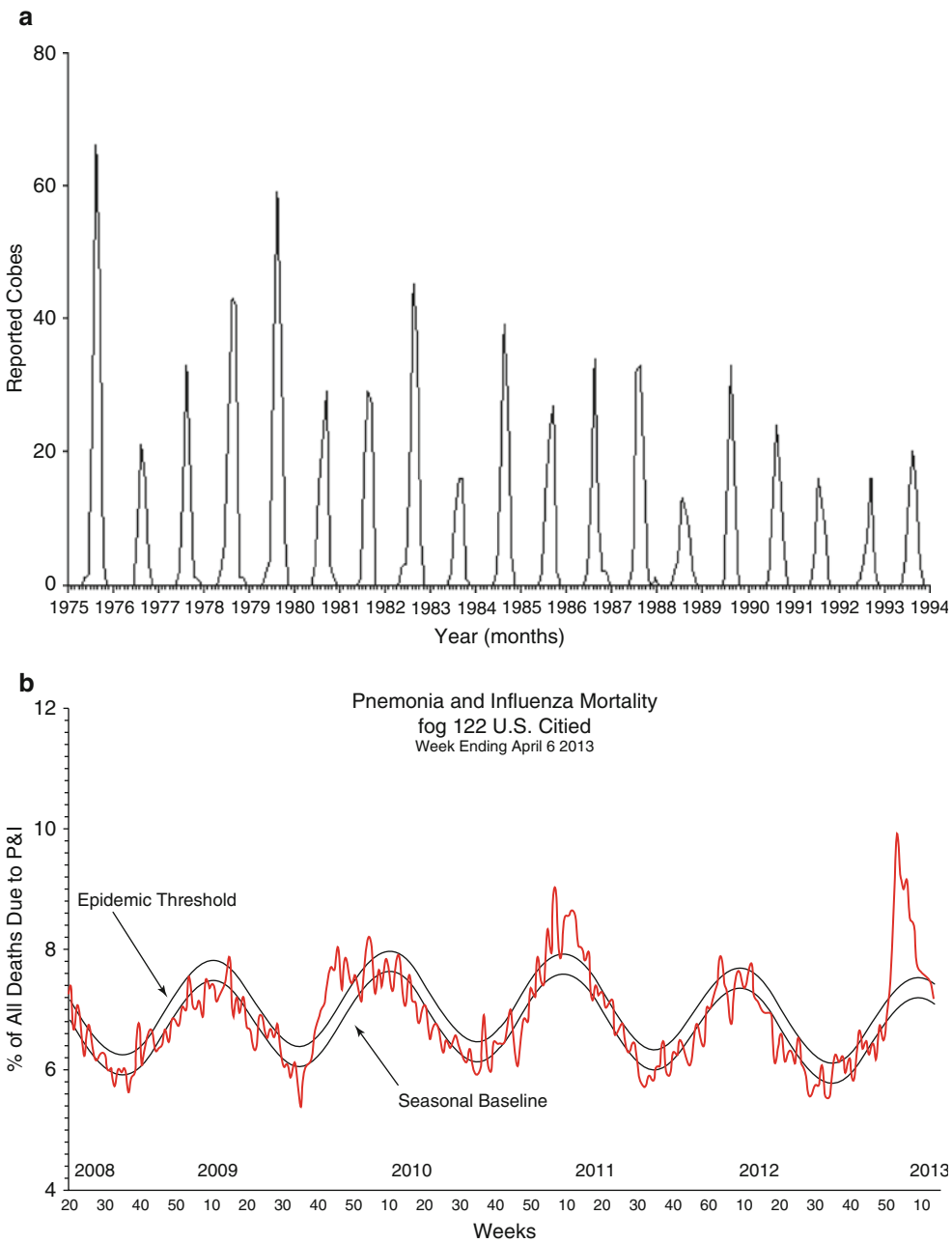


Fig. 1.3 Seasonal occurrence of selected viral diseases. Panel (**a**) Arboviral infections (of the central nervous system)—cases due to California serogroup viruses, by month, United States, 1975–1993 (Reproduced from Koo et al. [130]). Panel (**b**) Pneumonia and influenza mortality for 122 US cities, week ending April 6, 2013 (Reproduced from CDC [131])

that is predictable but might not occur every year in the same season.

Seasonality is one pattern that has been characteristic of many viral infections in the absence of widespread vaccine-induced immunity. Many of the childhood viral diseases (e.g., measles, rubella, mumps, chicken pox, polio, influenza gastroenteritis, etc.) and certain viral diseases of adults (e.g., vector-borne meningoencephalitis and influenza) show striking natural seasonal fluctuation.

For some of these illnesses, the explanation is obvious—rising incidence in summer parallels the resurgence of the vector population (e.g., for mosquito-borne encephalitis viruses, Fig. 1.3, Panel a) or the return of favorable conditions for replication (e.g., for enteric viruses) during warmer weather. For others (many respiratory infections), the conventional explanation is that increases in the winter reflect a combination of environmental factors (temperature and humidity) that both directly enhance the viral replication and transmissibility and indirectly lead to more conducive host behavior (more time spent indoors under artificial conditions of heat and ventilation). For a number of the diseases where vaccines have been effective at radically decreasing the incidence, the seasonality is barely or no longer discernible.

8.3.2 Endemic and Epidemic Occurrence

Infection and infectious diseases occur in populations in different patterns. Incidence rates may be constant or may show seasonal or secular trends. When the pattern of a given condition is stable or constant over a period of years, it is usually considered *endemic*. A number of chronic viral infections have affected certain populations in more or less the same pattern for decades; although their patterns may be distinctive in different subgroups, infections with herpesviruses, like cytomegalovirus, Epstein–Barr virus, and HHV-6, have largely remained endemic. Some could even be considered *holoendemic*—affecting entire populations, nearly universally and more severely in childhood and less so in older individuals. In contrast, an *epidemic* or outbreak of disease is recognized as the occurrence of cases in excess of the number expected for a population based on its past experience. The definition of "excess" is an arbitrary one and depends on the relative concentration of recent and previous cases in the place, time period, and population group of interest. In a country or region where a naturally occurring disease has not been seen for years, a few instances (e.g., encephalitis cases in summer) or even a single case (e.g., of poliomyelitis anywhere in the Western Hemisphere or Japanese B encephalitis in a country where none has been documented for years) could be deemed an epidemic. On the other hand, a large and rising number of cases of winter respiratory illness (e.g., due to the introduction of a new influenza strain) may signify normal seasonal fluctuation. For that pattern to be declared an epidemic usually requires application of more sophisticated criteria (i.e., deaths from influenza and pneumonia in 122 cities exceeding established threshold based on a 5-year average), for example, with the 2012–2013 season (Fig. 1.3 Panel b). When several continents are involved, as is the case with the global distribution of HIV/AIDS, the disease is said to be *pandemic*.

Three essential requirements for an outbreak of viral disease are the presence of an infected host or contaminated reservoir, an adequate number of susceptibles, and an effective method of contact and transmission between them. If the agent is not endemic within the community, then the introduction of an infected person, animal reservoir, or vector of transmission is needed to initiate a naturally occurring outbreak. While the infection may have long been endemic in some remote place, an accident of nature (e.g., importation of an animal carrying the agent) or change in human behavior (e.g., a lapse in hygienic practice in a hospital) triggers its emergence in a new location. This is particularly important in an island or isolated population group, where a virus disappears after no more persons remain susceptible, if persistent viral excretion does not occur to permit infection of newborns. Rubella, for example, disappeared from Barbados for 10 years despite an accumulation in the number of susceptibles to a level representing about 60 % of the population and despite the existence of a large tourist trade [132]. The introduction of more susceptibles or of more infected persons may tip this balance. On the other hand, antibodies to viruses characterized by persistent or recurrent viral excretion, such as herpesviruses and adenoviruses, have been present in every population thus far tested, no matter how remote or isolated [133].

Of recent, an increasing concern is a possible deliberate introduction of an agent capable of spreading mass illness and death. The leading viral candidates for use in an attack of bioterrorism (i.e., those causing smallpox, hemorrhagic fevers, arboviral encephalitis, or a severe pulmonary syndrome) are those for which the target population has little or no immunity. To be effective as an agent of bioterrorism, the proportion of susceptibles to infection with the candidate would need to be high, and the pattern and magnitude of the ensuing epidemic would therefore be particularly difficult to predict.

A critical characteristic of populations that strongly influences its experience with infectious diseases in general and the occurrence of an epidemic in particular is *herd immunity*. The herd immunity level is the cumulative proportion of persons immune to a given disease within a community. This proportion is, in turn, highly dependent on such variables as the probability of contact between a source of infection and the susceptible person, the portal of entry accessible, the contagiousness of the agent, and the degree of individual host immunity (all of which are often quantitatively summarized as the *basic reproduction number* (*or ratio*)). The term refers to the average number of new cases of infection transmitted by an index case during its interval of infectivity (see Chap. 5) [134, 135]. High prevalence of protective antibody to a virus among persons in a given community makes an outbreak with that virus most unlikely. Herd immunity to highly communicable infections such as measles, mumps, rubella, and influenza appear to require levels of antibody at least 75 % and even as high as 94 % to be effective (Table 1.7).

Table 1.7 Basic reproduction numbers and herd immunity thresholds for selected vaccine-preventable viral diseases

Disease	R_0	Herd immunity threshold (%)
HIV/AIDS	2–5	–
Influenza (1918 A/H1N1)	2–3	–
Measles	12–18	83–94
Mumps	4–7	75–86
Polio	5–7	80–86
Rubella	6–7	83–85
Severe acute respiratory syndrome (SARS)	2–5	–
Smallpox	5–7	80–85

Adapted from [136–140]

In an open college community, a preexisting level of immunity to rubella of 75 % failed to prevent an outbreak of this disease [141]. In a rubella outbreak among military recruits with a 95 % level of immunity, 100 % of the susceptibles were infected [142]. Close and prolonged contact is apparently extraordinarily efficient at spreading infection. Other principles are also worth emphasizing: (1) the concept of herd immunity is even less valid where several strains of virus exist and cross protection is not complete; (2) even the identical strain of virus that does not naturally confer complete immunity (e.g., certain herpesviruses) may reinfect; (3) reactivation of latent infection may produce disease, especially in immunocompromised hosts; and (4) the presence of antibody in the forms usually measured for such persistent viruses as HIV or hepatitis C indicates that humoral immunity is incomplete at best.

9 Investigative Approaches

9.1 Descriptive Epidemiology

The first steps in understanding infection and disease in populations constitute so-called descriptive epidemiology. It generally involves integrating the data that best characterize the phenomenon under investigation in the terms discussed in the preceding sections: the agent, environment, and host; the distinctive pathogenetic features; the patterns of occurrence in time and place; and the mode(s) of transmission. The technologies for detecting and defining the agent, quantifying environmental conditions, and profiling the immune status of the host have all been advancing at an exceedingly rapid pace. So have the noninvasive and imaging procedures for characterizing the clinical and pathophysiologic features of the disease. They have facilitated the pinpointing in time and location of cases of infection or illness, often revealing early key information about the origins and the mode of transmission of infection.

The next steps after cases are recognized involve systematically defining, counting, and reporting their occurrences; tabulating their frequencies; comparing their rates; graphing their trends; and evaluating and communicating the results of these efforts. The usual approaches for capturing and interpreting these events in the context of public health and disease control come under the broad heading of surveillance, which is covered in detail in Chap. 4.

9.2 Analytic Epidemiology

Beyond the collection of data for descriptive and surveillance purposes, insight into infectious disease at the population level also emerges from more sophisticated computational and pictorial representation of the salient events and relationships. Hypothesis testing and other formal evaluation of causal relationships, exploration of co-determinants of infection and illness, and recognition of patterns of occurrence all involve rigorous comparisons of data from exposed, infected, and/or diseased individuals with similar data from unexposed or unaffected individuals. That form of inquiry has come to be called analytic epidemiology, the basic methods of which are summarized below. Finally, in conjunction with these numerical and graphical methods, advances in the theory and methods of mathematical statistics have refined empirical and predictive models of virus–host adaptation, transmission and vector dynamics, incidence, epidemic trajectories, and other phenomena of infectious disease. Chapter 5 is a concise view of current approaches to modeling of viral transmission dynamics.

The analysis of the results assembled and integrated during the data gathering and descriptive phase primarily involves evaluating relationships or associations with standard measures. These measures and the investigative approaches to estimating them are summarized very briefly here; more elaborate treatment of the epidemiologic and statistical principles underlying them can be found in any of several textbooks on epidemiology as noted in Sect. 1.

9.2.1 Cohort Studies

The search for associations in epidemiologic data often consists of comparing rates of infection in cohorts of individuals exposed and unexposed to a specific risk factor or rates of disease in cohorts of infected and uninfected individuals. Cohort studies may be cross-sectional or longitudinal in design. In the former, the exposure and the outcome are measured in the population at a single time point. There are many relationships for which the timing of the exposure relative to the disease cannot be established through cross-sectional observation; however, there are many others for which the pathogenesis is understood or the exposure is unambiguously antecedent to the outcome (e.g., genetically mediated rapid progression of HIV infection or shingles in an individual with serologic evidence of VZV infection). In contrast, longitudinal cohort studies are often more powerful because the temporal relationship between the exposure and the outcome can be explicitly established. Although ulcerative inflammation due to HSV-2 is a risk factor for acquisition of HIV infection, it could also be a more prominent consequence of HIV-induced immunosuppression. Only longitudinal observation of precise temporal relationships between the onset of these two infections and the timing of their clinical manifestations would allow definitive inferences about causality.

The most informative measure of association in a cohort study is usually the *relative risk*, used synonymously with risk ratio or rate ratio. Relative risk is estimated as the ratio of the rate of the event (infected or ill) among exposed or infected persons, respectively, to the rate of such an event in the unexposed or uninfected persons. In cohort studies in which all or representative samples of individuals exposed and unexposed to a virus are observed for a period of time until some proportion of each sample develops disease, a

Table 1.8 Standard analytic table for estimating relative risk and relative odds

	Infected/ill	Uninfected/well	
Exposed/infected	a	b	$(a+b)$
Unexposed/uninfected	c	d	$(c+d)$
	Affected $(a+c)$	Unaffected $(b+d)$	Total $(a+b+c+d)$

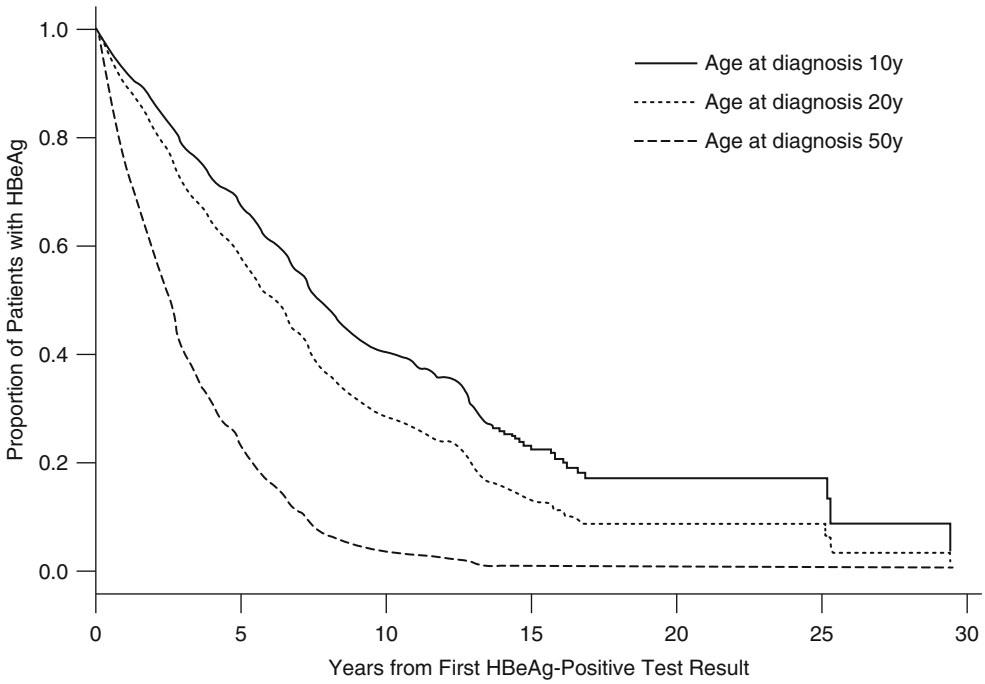


Fig. 1.4 Predicted survival curves (time from first HBeAg-positive result to clearance) at ages 10, 20, and 50 years. Significant covariates included in the model are age at diagnosis of HBsAg (including a nonlinear effect), an interaction of initial recorded status of HBeAg (positive or negative) and age, and the number of HBeAg measurements recorded. The overall probability of clearing HBeAg within 10 years was 72.5 %. In those who cleared HBeAg, the median time to clearance was 5.6 years (range, <1 to 29.4 years). Older carriers were significantly more likely than younger ones to clear HBeAg ($P<0.001$) (Adapted from McMahon et al. [143])

"true" relative risk is calculated as the ratio of the eventual cumulative incidences in the groups with and without exposure or $[a/(a+b)]/[c/(c+d)]$ (Table 1.8).

For conditions that develop over variable lengths of time, if the actual time between exposure/infection and disease is known, it is often preferable to incorporate that time element into the estimate relative risk. That can be done either graphically in survival (Kaplan–Meier) plots (Fig. 1.4) or numerically by application of statistical techniques of which a very useful and popular one is known as a (Cox) proportional hazards regression, yielding a *relative hazard*. Several useful pieces of information about the timing of events can be extracted from the survival curves. As in other regression models, a proportional hazards model can include multiple factors to be assessed for their independent contribution to the outcome (disease).

9.2.2 Case–Control Studies

When an investigation can only be done feasibly on infection or disease that has already occurred following presumed exposure to some etiologic agent in the past, properly designed comparison of those exposed and affected (cases of infection or disease) with those exposed and unaffected (controls) can provide a valid measure of association. When the available cases and, for efficiency, only a small subset of all the non-cases are compared, the putative causal relationship is measured as the *relative odds*, a term synonymous and interchangeable with the *odds ratio*. Based on mathematical principles, for diseases that are uncommon in the population, the relative odds, calculated as $[a\times d/b\times c]$, represent a close approximation to the relative risk (Table 1.8). The case–control study design is especially productive in epidemic situations where the investigation needs to be structured around cases that are reported or sought in the absence of a clear causal exposure. The analysis of case–control studies is usually performed with the technique of logistic regression, which can accommodate independent variables other than the putative causal factor. The major limitation is the many forms of bias that can distort the estimate of the strength of the key relationship, due to difficulties in selecting and assessing study subjects with the tight comparability necessary for proper analysis.

9.3 Investigation of an Epidemic

This brief introduction to the strategy and tactics of epidemic investigations is best supplemented by more extensive guidance found elsewhere [144–146]. From the earlier discussion of the origin and nature of epidemics, it should be clear that no two are exactly alike, but just

Table 1.9 Investigation of an epidemic

1. Determine whether an outbreak is occurring
2. Verify the diagnosis
3. Establish a case definition
4. Enumerate cases
5. Conduct descriptive analyses of the preliminary data
6. Develop hypotheses about the cause of illness and the source of infection
7. Evaluate the hypotheses with analytic methods
8. Conduct additional epidemiologic, environmental, or laboratory studies
9. Develop and implement prevention and control measures
10. Communicate the findings

Adapted from Dicker et al. [145] (CDC publication, no copyright)

as there are patterns to endemic occurrence of disease, there are patterns to epidemics. A systematic approach to their investigation should take account of those patterns by incorporating the sequence of steps outlined in Table 1.9, although this list is neither exhaustive nor in strict priority order of execution.

Outbreaks may come to attention in a variety of ways. An insightful clinician may suddenly see one or more unexpected cases of a syndrome or atypical presentations of infection, just as happened at the onset of the HIV/AIDS epidemic [147]; or a laboratory may identify an unusual viral strain in the course of routine testing (e.g., a novel influenza variant) [148]; or a health department officer may recognize a cluster of cases of, say, norovirus gastroenteritis as multiple entries in computerized syndromic surveillance system [149]. With any such initial event, it may not be possible to establish a diagnosis only at the level of a clinical syndrome and not with etiologic specificity. At this initial stage, a somewhat specific but simple working definition should include key epidemiologic and clinical features for the purposes of case finding. This definition can be altered in its sensitivity or specificity later, when the spectrum of clinical features has been clarified and laboratory studies have been completed. The definition is primarily for the purposes of beginning to enumerate cases. This enumeration is accompanied simultaneously with the organization and analyses of the clinical data and construction of a plot (epidemic curve) of cases according to onset or recognition and/or a plot of the location of cases. Categorization by occurrences by infection, case, or death may provide information about the seriousness of this outbreak relative to previous ones.

Even at this early point, if the pattern of cases or other information reveals a likely mode of transmission, control measures should be instituted. Not surprisingly many epidemics of viral infection result from person-to-person spread, particularly by the respiratory route, in open communities or in relatively closed populations like health or extended care facilities. Vector-borne spread also accounts for a significant portion of epidemic viral infection throughout the world (see Chaps. 7, 8, 9, 14, 15, and 16,). Common source outbreaks of viral infections from water, food, milk, or other environmental sources have not historically been as common as those due to bacterial infections. However, such outbreaks have been recognized increasingly in recent years. Some examples include spread of adenoviruses by tonometers in eye clinics or in swimming pools, hepatitis A by public water supplies or by seafood, or enteroviruses by fecally contaminated water, food, or milk (see Chap. 17).

As the nature, magnitude, mode of transmission, and likely etiologic agent of the outbreak become clearer, the analyses can be refined and focused on more conclusive tests of hypotheses about individuals or other sources and the modulating factors such as age, sex, occupation, recreation, and other geographic or social characteristics of cases. The results of these analyses may assist in excluding or adding cases and focus control measures on individuals most directly affected as well as those at continued risk. The epidemiologic discovery of the cause and other features of the outbreak along with the implementation of control measures will further oblige and enable the investigative team to communicate effectively with the numerous stakeholders in a typically quite visible public health event.

10 Control and Prevention

The basic strategy for controlling a disease is to break one or more links in the chain of causation or pathogenetic continuum. Any such a strategy must rest on the fundamental knowledge of the agent, host, and environment for the particular infection; the control may be physical, chemical, or biological in nature. In the simplest terms, control at the level of the agent usually means incapacitating or destroying it with a physical force as with ultraviolet or light or freezing. A variety of chemicals can also be used externally, particularly on inanimate surfaces (i.e., virucidal disinfectants such as detergents, methylene blue, and chlorine or other compounds that depend on the activity of hypochlorite). At the level of the environment, the strategy might involve an engineering solution such as improving water supplies or sewage disposal or installing negative-pressure ventilation systems, or it might involve avoiding, suppressing, or eradicating the vector population using a widely sprayed insecticide or some other intervention that alters the vector habitat. Effective prevention can also be achieved at the personal level with behavioral intervention to prevent contact (e.g., isolating or cohorting infected individuals in separate rooms, wearing protective clothing such as masks or gowns, applying a topical insect repellant, or washing hands with any of a variety of antiseptic agents). Because of space limitation, for more information on the principles and practices of isolation and barrier, sanitation, disinfection and antisepsis, environmental engineering,

and vector control, the reader is referred to more general texts and references on selected topics here; many others on these numerous topics are available [95, 150–153].

The remainder of this section will concentrate on strategies that depend on biological activity of pharmaceutical agents that can be injected, ingested, or topically applied in humans. These are antiviral products that target specific strains or broad classes of viruses and vaccines and immunobiologics that capitalize on specific host responses to particular viruses.

10.1 Therapy and Chemoprophylaxis

Strategies for designing antiviral agents focus on the numerous vulnerable points in the replicative cycle of a virus that are, ideally, distinct from any point along the synthetic pathways of the human host. There is a growing list of candidate drugs with established clinical antiviral efficacy, and new compounds can now be designed in silico with computer programs that can produce exquisitely precise models of protein–protein interactions that help predict their likely biologic effects. Of course, as promising as these advances are, the ideal is rarely achieved. Limitations still include the poor correlation of effects predicted by in silico, in vitro, or animal studies with those observed in humans, strain differences in response, easy emergence of resistance, and unforeseen acute toxicity. Delayed adverse consequences like oncogenicity and teratogenicity are also a concern.

Each chapter on individual viral infections provides more information about the antiviral pharmaceuticals in use or in trial for those viruses. For another review of antivirals used in specific infections, refer to Ref. [154]. Here simply for rapid reference and comparison is a summary tabulation of the diseases and viruses (other than HIV/AIDS, which is covered in greater depth in Chap. 43), the corresponding antiviral drugs available at the time of publication, their mechanism of action and/or stage of replication affected, and their use for treatment and/or prophylaxis (Table 1.10).

In addition to the antiviral agents covered here, several new candidates in familiar classes as well as new classes of drugs are under experimental and in some cases human investigation. They include numerous new drugs of several classes for HCV; cyclopropavir for CMV infection; a methanocarbathymidine compound active against several herpesviruses; a drug similar to cidofovir with activity against polyoma-, adeno-, pox-, and herpesviruses; favipiravir, which inhibits replication of influenza and probably arena-, bunya-, and hantaviruses; pleconaril and other drugs that inhibit picornaviruses; drugs targeting kinase pathways; and other agents with a broader antiviral spectrum, such as those that bind to the uniquely viral intermediary double-stranded RNA while initiating apoptosis [155–157].

10.2 Immunization

Each chapter on a viral infection for which an effective or promising immunizing agent is available includes details of that virus-specific immunization. This section presents

Table 1.10 Antiviral drugs licensed/generally available for human use

Condition	Virus	Agent	Mechanism of action	Treatment (Rx), prophylaxis (Px)
Cold sores, fever blisters, labial herpes	HSV-1	Acyclovir, ganciclovir, famciclovir, zanamivir, valacyclovir, vidarabine[a] foscarnet, and others	Nucleos(t)ide analogue, inhibits deoxypyrimidine kinase as a competitive substrate	Rx, Px
Genital herpes	HSV-2			
Chicken pox, zoster	VZV			Rx
Cytomegalovirus	CMV	Cidofovir, fomivirsen, foscarnet		
Influenza A	Influenza A virus	Amantadine, rimantadine	Interferes with ion channel protein (M_2) and uncoating	Rx, Px
Influenza A	Influenza A virus			
Respiratory syncytial virus	RSV	Rimantadine		Rx
Influenza A and B	Influenza	Oseltamivir, zanamivir	Blocks release by inhibiting neuraminidase	Rx, Px
Chronic hepatitis B	HBV	Adefovir, emtricitabine, lamivudine, tenofovir	Nucleos(t)ide analogue	Rx
Chronic hepatitis C	HCV	1. Interferon-α	1. Cytokine initiating intracellular immune response cascade	Rx
		2. Ribavirin	2. Nucleoside analogue	
		3. Boceprevir, telaprevir, simprevir	3. Inhibits replication by binding to the nonstructural protein, serine protease	
		4. Sofosbuvir	4. RNA polymerase	
Respiratory syncytial virus infection	RSV	Ribavirin	Nucleoside analogue	Rx

Reproduced and adapted from [155]
[a]Now only for ophthalmic use

general perspectives and more concrete information, including the objectives of vaccination, types of immunization for viral infections, schedules for immunizing target populations with agents licensed in the United States, prospects for eradication of viral diseases, and national and international programs concerned with immunization. For deeper treatment of the principles and practice of vaccinology, consult Ref. [158].

10.2.1 Active Immunization

Active vaccines are administered with the goal of stimulating antibody production by the host to provide a high degree and long duration of protection but with no or minimal accompanying illness. The full set of objectives for creating a good vaccine for active immunization is listed in Table 1.11. Both live and killed vaccines are used, and Table 1.12 compares the two types. Active viral vaccines containing live attenuated virus (measles, mumps, rubella, and smallpox viruses, poliovirus, adenovirus, and VZV) have generally been more immediately, broadly, and durably protective than killed vaccines or other constructs, especially when they are administered by the natural portal of entry to produce local immunity. However, there are a growing number of exceptions to that rule—live virus preparations that are less fully successful (e.g., VZV vaccine against herpes zoster, nasally administered influenza vaccine) while certain non-replicating types formulated as recombinants that appear to provide unexpectedly high protection (e.g., HBV and HPV vaccines). In the case of hepatitis A, both inactivated and live attenuated formulations are highly effective, although immunity generated by the latter may be somewhat longer lasting [159].

Limitations to the wide applicability of live vaccines include the difficulty of successfully attenuating the candidate strain without reversion to virulence, the avoidance of viral persistence and the risk of reactivation, and the elimination of possible oncogenicity. These have been major hurdles for vaccines against herpesviruses, and it is difficult to measure some of these attributes in the laboratory. Efforts to produce live vaccines with temperature-sensitive mutants that replicate in the upper respiratory but not in

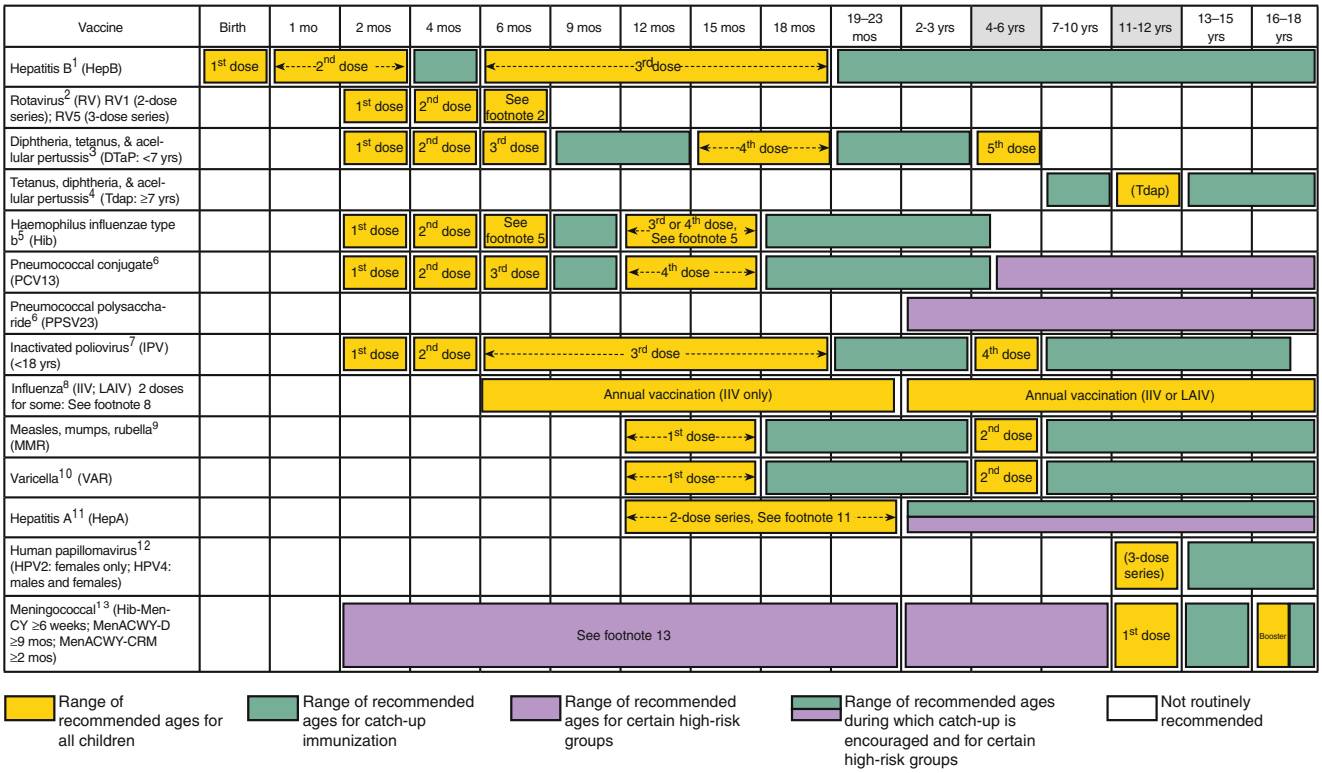
Table 1.11 Objectives for a vaccine

1. Elicit a good humoral, cellular, and/or mucosal immune response that correlates with protection against clinical disease and reinfection
2. Provide protection lasting at least several years and preferably a lifetime, similar to that induced by natural infection that leads to lifetime immunity
3. Result in minimal immediate side effects or adverse reactions or mild disease and result in no delayed effects (e.g., late reactivation, CNS involvement, or cancer)
4. Require a simple regimen for administration in a form and a schedule acceptable to the target population and the general public
5. Pass a favorable cost/benefit analysis, where the health and economic benefit of administration clearly outweighs the cost and risk of natural disease and the adverse consequences of administration

Table 1.12 Comparison of live and killed vaccines

	Live	Killed
Immune response		
Humoral antibody (IgG)	+++	+++
Local antibody (IgA)	+++	+
Cell-mediated immunity	+++	+
Duration of response	Longer	Shorter
Epidemiologic response		
Prevents reinfection by natural route	+++	++
Stops spread of "wild" virus to others	++	+
Some vaccine viruses (polio) spread to others	+++	0
Creates herd immunity if enough persons are vaccinated	+++	0
Characteristics of the vaccine		
Usually heat stable, may need to keep below freezing point until just prior to administration	++	0
Vaccine virus may mutate or increase in virulence	+	+
Antigenic site limited or lost during preparation (e.g., formalin treatment)	0	+
Contraindicated in immunosuppressed persons	+++	0
Side reactions:		
Systemic (viremia)	+	0
Local	0	++
Number of doses for successful take	1	2–3

The table is a simplification and may not apply to all vaccines. Some live vaccines, e.g., polio, are relatively heat stable. Knowledge of the presence of and degree of protection by cell-mediated immunity is inadequate for many vaccines



This schedule includes recommendations in effect as of January 1, 2014. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combinationvaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967).Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, i ncluding precautions and contraindications for vaccination, is available from CDC online (http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm) or by telephone (800-CDC-INFO [800-232-4636]).

This schedule is approved by the Advisory Committee on Immunization Practices (http/www.cdc.gov/vaccines/acip), the American Academy of Pediatrics (http://www.aap.org), the American Academy of Family Physicians (http://www.aafp.org), and the American College of Obstetricians and Gynecologists (http://www.acog.org).

Fig. 1.5 Recommended immunization schedule for persons aged 0 through 18 years—United States 2013. These recommendations must be read with the footnotes that follow [161]

the lung have culminated in the licensure of a cold-adapted nasal influenza vaccine recommended for use in healthy 2–49-year-olds.

A comprehensive overview of general immunization principles and recommendations can be found in Ref. [160]. The schedule for immunization of immunocompetent infants, children, and adolescents is shown in Fig. 1.5 [161], and for immunocompetent adults in Fig. 1.6 [211]. They reflect recommendations that took effect in 2013 and will obviously be modified as new agents and regimens are found to be effective.

The above pages of the CDC website are the definitive sources of information about the requirements for immunization and details of administration, precautions, contraindications, and other aspects in the United States. References to CDC recommendations are also available for immunization in other specific situations: health-care personnel [162], special health conditions [163], pregnancy [164], and international travel [165].

10.2.2 Passive Immunization

Passive immunization with an Ig preparation is an expedient useful in short-term prevention primarily when it can be administered soon (preferably within hours) after exposure and when it contains a sufficiently high titer of antibody that will be effective against the agent.

Some preparations are derived from persons known to be convalescent from the disease and from persons hyperimmunized against it or by selecting only donors shown to have high antibody titers. Passive immunization is generally limited to well-defined exposures to rabies virus or in immunocompromised patients who are susceptible to HAV, HBV, VZV, CMV, and vaccinia (unlikely in the absence of smallpox immunization but potentially useful if vaccinia virus gains acceptance as a carrier for other antigens).

10.3 Disease Eradication and Elimination

Smallpox was the first and only disease to have been officially declared eradicated from the earth. From the moment of that historic accomplishment in 1977, this consummate success of the WHO eradication program has inspired initiatives to replicate it with other diseases. The definition of *eradication*, telegraphed in Table 1.13, can be more fully understood in

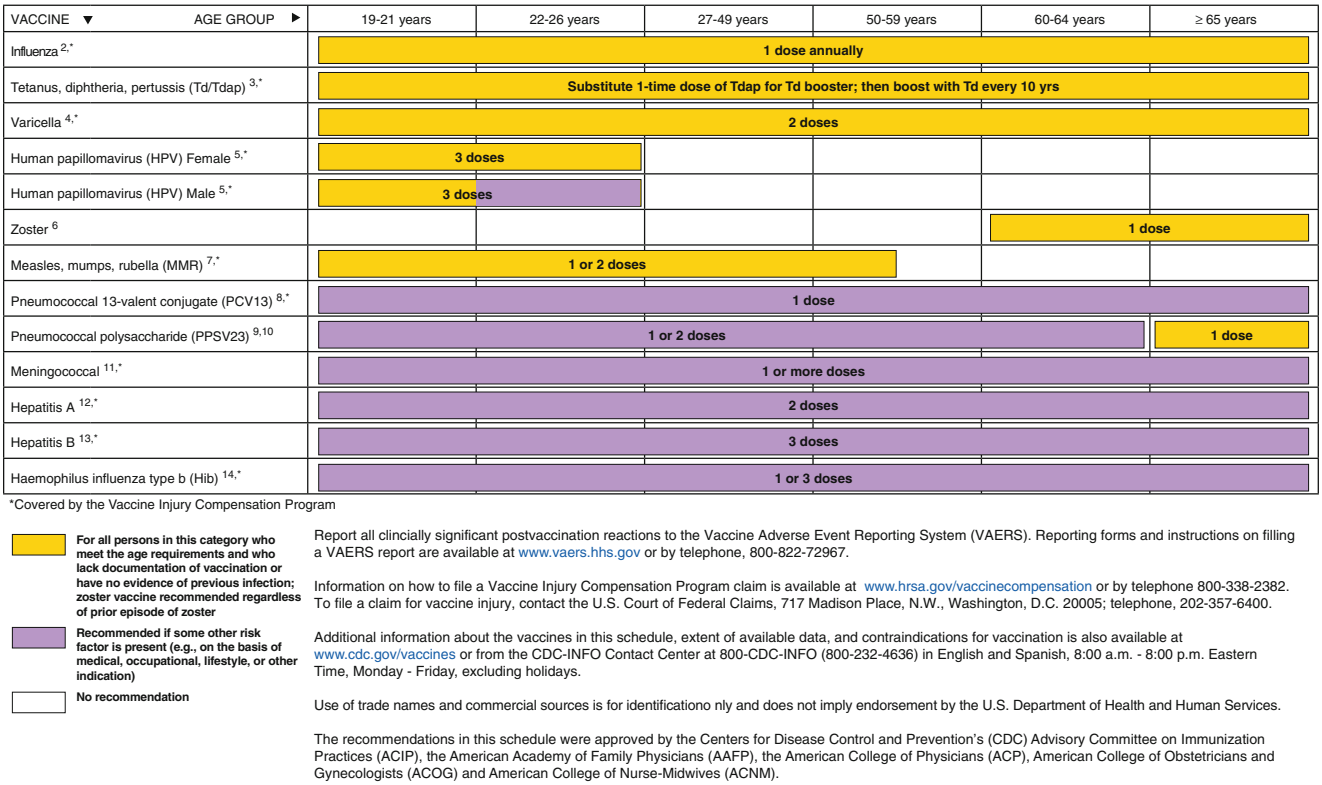


Fig. 1.6 Recommended adult immunization schedule by vaccine and age group [211]

the context of viral infection as "…disappear[ance] from all countries of the world because transmission of the causative organism has ceased in an irreversible manner" [166]. A less ambitious goal, *elimination*, denotes disappearance of the causal agent within a large geographic area; this goal has often been viewed as an intermediate step toward eradication. The critical distinction made in Table 1.13 is that once a disease is eradicated, it is no longer necessary to maintain the elaborate public health apparatus required for ongoing surveillance and control. The implications for achieving either result in practice are that (1) every real or potential occurrence in every location within the target area must be taken seriously, (2) the infection and the interventions to control it must be carefully monitored, (3) program structure and function must be nimble and thorough in response to any suggestion of difficulty or failure, and (4) the rising cost of preventing each successive case cannot be allowed to justify diverting resources away from the goal [167].

Only a few other viral diseases have come close enough to meeting the criteria for potential eradication or elimination to receive serious consideration. In 1993 the International Task Force for Disease Eradication promulgated its list of recommended target diseases for eradication or elimination, and the Task Force recommendations and assessment were updated

Table 1.13 Disease eradication

Definitions
Eradication
Zero disease globally as a result of deliberate efforts
Control measures no longer needed
Elimination
Zero disease in a defined geographic area as a result of deliberate efforts
Control measures needed to prevent reestablishment of transmission
Criteria for assessing the eradicability of a disease
Scientific feasibility
Epidemiologic susceptibility (e.g., no nonhuman reservoir, ease of spread, naturally induced immunity, ease of diagnosis)
Effective, practical intervention available (e.g., vaccine, curative treatment)
Demonstrated feasibility of elimination (e.g., documented elimination from island or other geographic unit)
Political will and popular support
Perceived burden of the disease (e.g., extent, deaths, other effects; relevance to rich and poor countries)
Expected cost of eradication
Synergy of eradication efforts with other interventions (e.g., potential for added benefits or savings)
Need for eradication rather than control

Reproduced from Ref. [167]

Table 1.14 Diseases considered as candidates for global eradication by the International Task Force for Disease Eradication

Disease	Current annual toll	Chief obstacles for eradication	Conclusion
Measles	780,000 deaths, mostly among children	Lack of suitably effective vaccine for young infants	Potentially eradicable
Mumps	Unknown	Lack of data on impact in developing countries; difficult diagnosis	Potentially eradicable
Poliomyelitis	2,000 cases of paralytic disease; 200 deaths	Insecurity; low vaccine coverage; increased national commitment needed	Eradicable WHA 41.28 (1988)
Rubella	Unknown	Lack of data on impact in developing countries; difficult diagnosis	Potentially eradicable
Diseases/conditions of which some aspects could be eliminated			
Hepatitis B	250,000 deaths	Carrier state, infections in utero not preventable; need routine infant vaccination	Not now eradicable, but could eliminate transmission over several decades
Rabies	52,000 deaths	No effective way to deliver vaccine to wild animals that carry the disease	Could eliminate urban rabies

Reproduced from Ref. [169]

in 2008 (Table 1.14) [168, 169]. Global efforts against both poliomyelitis and measles have been the most concerted. The successes and setbacks are covered in the respective chapters on the two conditions (Chaps. 13 and 23).

Although the original Task Force and those who have updated their work acknowledged certain key obstacles, in reality, even when the commitment is strong, funding is seldom entirely sufficient for the tasks at hand, motivation of all key stakeholders is difficult to sustain, and political and social insecurities remain an unpredictable threat. The intensive effort to eradicate polio has been a test case. In 1988 WHO formally initiated its campaign to eradicate poliomyelitis. Under the overall leadership of WHO, it and numerous public and private organizations (e.g., CDC, Rotary International, UNICEF, and the Bill and Melinda Gates Foundation) have persevered in this mission for more than 20 years [170]. It is noteworthy that even before the inception of this more coordinated effort, in 1979 Rotary International began its remarkable commitment to polio eradication, and for three decades, through its worldwide chapters, it performed tireless vaccine campaign work that has recently captured the attention of major news organizations [171, 172, 176]. By 2006 polio remained endemic in only four countries, whereupon gains continued but began to be punctuated by periodic setbacks. Then new blows began to be struck in late 2012 as a result of lethal attacks on healthcare workers conducting polio immunization campaigns in Pakistan and Nigeria and even on their police escorts [173], as well as introductions into countries where war had degraded the public health infrastructure. Continual political and social unrest has fueled the spread of lies about motives of the health workers and the consequences of immunization [174]. All of this turmoil has seriously threatened the eradication program.

Unfortunately, even in the United States, where widespread if not universal elimination of other childhood viral diseases is at least imaginable, there have been very recent resurgences of measles [175], mumps [176], and chicken pox [177], most likely for a combination of reasons: waning immunity despite what had been deemed adequate vaccination recommendations and coverage, gaps in coverage among minority and other populations, and more general resistance to vaccination stimulated by negative publicity in social media along with pockets of objection on religious grounds.

10.4 Programmatic Approaches to Immunization

10.4.1 United States

Creating, testing, producing, licensing, recommending, and monitoring vaccines share many aspects with analogous steps involved in pharmaceutical development and marketing. Descriptions of those elaborate processes are beyond the scope of this chapter. On the other hand, because vaccines are administered almost entirely to basically healthy individuals, often on a global population scale, various distinctive programmatic features of their use are worth considering here briefly. The following summary of the major domestic and international programs involved in vaccine development and delivery may help the reader to appreciate the enormous commitment to immunization for prevention and control of viral infections in general and to understand how a vaccine for any specific infection covered in this text fits into this larger context.

In the United States, besides certain private sector pharmaceutical manufacturers, the National Institute of Allergy and Infectious Diseases [a component of the National Institutes of Health within the Department of Health and

Human Services (DHHS)], the Department of Defense, and other agencies conduct and/or support a broad variety of basic microbiological and immunological research fostering the creation of new and better vaccines. The Food and Drug Administration oversees the development and licensure of all vaccines for human use; through many years of legislation, regulation, and policy-making, this agency has built an elaborate system for ensuring that the products of vaccine manufacturers are safe and effective. Such pre-market design, development, and production activities are beyond the scope of this chapter. Although these Federal agencies remain closely involved with monitoring and reviewing the safety and effectiveness of vaccines once they are licensed and distributed, the National Vaccine Program and CDC are the DHHS components in the US Federal government that have primary authority for implementing and monitoring their use in populations. The DHHS and particularly the CDC are engaged in other activities related to vaccine use, but the following paragraphs highlight its principal responsibilities.

National Vaccine Program Office

This group oversees and coordinates all of the DHHS agencies and offices involved with vaccine development and utilization. In 2010, in part with a view toward achieving the immunization-related objectives established by the Federal government in *Healthy People 2020*, the NVP/DHHS published *the 2010 National Vaccine Plan*, a carefully articulated set of goals and objectives and recommendations on how to reach them [178]. The five overarching goals of the plan are to (1) develop new and improved vaccines; (2) enhance the vaccine safety system; (3) support communications to enhance informed vaccine decision-making; (4) ensure a stable supply of, access to, and better use of recommended vaccines in the United States; and (5) increase global prevention of death and disease through safe and effective vaccination. There also a separate implementation plan, which details the tactics to be pursued in meeting the goals [179].

Surveillance of Vaccine-Preventable Diseases

Through its long-standing relationships with state and local health departments, CDC has implemented increasingly elaborate systems and methods for reporting of selected infectious diseases, a number of which are viral and a subset of which are vaccine preventable. These systems are reviewed in detail in Chap. 4.

Vaccines for Children Program (VFC)

In 1994 the Federal government initiated and began to fund this program to provide free vaccines to children for whom they would otherwise be unaffordable [180]. As administered by CDC, the program currently provides vaccines against the following viral infections: hepatitis A, hepatitis B, human papillomavirus, influenza, measles, mumps, poliomyelitis, rotavirus, rubella, and varicella zoster. There is general agreement that VFC had been a vital force in ensuring relatively high levels of immunization in vulnerable populations, thereby contributing to the major successes in reducing vaccine-preventable diseases in the past two decades.

Advisory Committee on Immunization Practices (ACIP)

This committee is chartered by Federal law [181] to advise CDC and, in effect, all government agencies and the public at large about the appropriate use of vaccines to control those diseases for which immunizing agents are available. The committee meets regularly to review statistics on vaccine-preventable diseases; new experimental and other research findings relevant to vaccine safety and efficacy; information about current vaccines, including labeling and package inserts; newly licensed products; policies and guidelines of other organizations; cost considerations; and other aspects of immunization policies and programs. Recommendations may be forthcoming on any of those topics; in addition, recommendations may also cover for modification of schedules, for administration of vaccines in the Vaccines for Children Program, or for introduction of new vaccines into the program. This advice carries heavy weight throughout the public health, health-care provider, public and private health insurance, and legal communities. The primary legal authority for matters of public health and disease control is vested in the states, and most of them follow ACIP guidelines closely.

Vaccine Adverse Event Reporting System (VAERS)

In 1986, congressional legislation required CDC and FDA to develop this system for receiving, monitoring, and responding to reports of potential side effects and complications of immunization [182, 183]. Every effort is made to document any such untoward event following administration of a licensed vaccine, regardless of the degree of certainty about the causal relationship to the vaccination. Each year, the system receives some 30,000 reports of events, the vast majority of which are mild.

10.4.2 International

WHO

In 1974 the World Health Assembly, encouraged by the success of the smallpox eradication campaign, created the Expanded Program on Immunization (EPI) [184] to ensure that children everywhere would receive routine immunizations. The early goals of the program were to assist in developing the appropriate immunization policies and systems. In its evolving role, it has promoted the key objectives of service delivery, vaccine storage with temperature control (cold chain maintenance), timely vaccine distribution, surveillance of disease and vaccination rates, health-care personnel training, and efficient program management.

More recently (2006), WHO and UNICEF produced the Global Immunization Vision and Strategy (GIVS) [185] aimed at reducing morbidity and mortality from vaccine-preventable diseases during the decade ahead, not just in children but in all segments of the population. The strategy includes immunizing more broadly, introducing a range of new vaccines and technologies, integrating vaccination and other preventive health care, and coordinating programs on a global level. The overall strategy contains numerous goals from which countries can select to tailor their own specific programs. Within only a few years after its adoption, GIVS has been successful in stimulating the establishment of a number of national immunization plans.

GAVI

As a culmination of the World Economic Forum in Davos, Switzerland, at the beginning of the new millennium, major stakeholders in the global immunization (UN agencies, donor governments, vaccine industry leaders, aid organizations, and others) formed a consortium called the Global Alliance for Vaccines and Immunization (GAVI). The mission of this entity is to bring new vaccines to all children of the developing world. The specific goals include intense focus on the more than 20 million children worldwide in poor areas who would otherwise remain unvaccinated against vaccine-preventable diseases, acceleration of delivery of new vaccines to the poorer countries as soon as possible after they are available in the wealthier ones, and channeling support for academic and industrial research on new vaccines targeted to the developing world.

Early GAVI efforts in the realm of viral diseases concentrated on vaccines against hepatitis B and yellow fever. Lately, attention has turned to delivery of rotavirus, the second dose of measles, human papillomavirus, Japanese encephalitis, and rubella vaccines. Two examples of current initiatives include the intention to immunize 700 million children against measles and rubella by 2020 and plans for administering HPV vaccine to 180,000 preadolescent girls in the first phase of a campaign to protect girls in many developing countries against cervical cancer. The alliance has depended heavily on grants and donor government pledges along with private philanthropic contributions, but it has substantially capitalized on more innovative financing for purchases of existing vaccines and for mutual assurances about the future availability of vaccines and the funds needed to purchase and deliver them. More details about the goals and accomplishments of GAVI to date can be found at Ref. [186].

Bill and Melinda Gates Foundation

As a powerful force in the quest to control vaccine-preventable diseases, for years this foundation has supported both traditional and innovative approaches to the development and delivery of vaccines for the places in greatest need [187]. The strategy incorporates five themes: making routine vaccines available, introducing new vaccines as they become available, using innovative and market-based approaches to financing and implementing immunization programs, promoting decisions about the deployment of vaccines based on scientifically sound evidence, and advocating for the support for vaccine programs by other stakeholders. The Supporting Independent Immunization and Vaccine Advisory Committees Initiative is one of those funded by the Gates Foundation to promote National Immunization Technical Advisory Groups (NITAGs) [188]. These groups provide recommendations on immunization policies and programs (e.g., schedules for administration of existing vaccines, improved coverage, and introduction of new vaccines) [189].

10.5 An Emerging Challenge to Immunization

Government and nongovernment organizations alike are engaged in an enormous multipronged worldwide immunization enterprise. There are many natural and legitimate concerns about the prospects for continuing success with each vaccine-preventable disease. The obstacles in every domain—scientific, political, economic, cultural, and others— are formidable. It was especially distressing to learn that one of those obstacles, opposition on religious/ethnic grounds, had motivated the murder of innocent Pakistani and Nigerian health workers in 2012–2013 [190, 191]. In retrospect, such extreme but, hopefully, isolated acts should not be all that surprising as part of the spectrum of social or religious opposition to vaccination campaigns in countries with poorly educated populations. However, on a more ominous note, beginning in the 1990s, the United States and other developed countries have witnessed a gradual increase in the numbers of parents who are refusing to permit their children to receive required routine immunizations. Because the refusals have tended to concentrate among certain subsets of the population who may be clustered geographically [192, 193], the relatively higher proportions of children whose parents have denied them vaccination have led to outbreaks of vaccine-preventable disease [194]. The resulting increased risk of such diseases as measles engenders particular concern because children unvaccinated against them not only are vulnerable in their own right but also pose significant risk to their contacts who may remain unprotected—because of exemption from vaccine requirements, a medical precaution or contraindication for live vaccine, vaccination exclusion for young age, or inadequate response to vaccine [195].

Religious beliefs have often been cited reasons for requesting exemption, but other anti-vaccine forces are at work too [196]. Although incidents with contaminated products had raised largely transient concern in the more distant past [197],

it was the reported but now thoroughly discredited research on the role of vaccination as a cause of autism that probably accounted for the first more serious and lasting rupture in public confidence in the benefits of immunization in general [198, 199]. The news media, in their predilection for controversy, have not always presented a properly *iunbalanced* view of the facts and claims [200]. Mass migration to the Internet as a primary source of health information has led to a proliferation of online websites highlighting anecdotal attributions by parents of various other adverse events to vaccines. While unsupported allegations are unfortunate, their appeal to parents of ill children as easy explanations or as sources of comfort or even justifications for tangible compensation is also understandable. However, more disturbing are print- and web-based testimonies by supposed experts in field of vaccines including radical, unfounded assertions about research that links vaccination to various deleterious biological and clinical consequences. Some of these arguments appear to have arisen from distrust of government [201]. Other claims are likely motivated by anecdotal experiences, favorable publicity, and/or financial benefits that may accrue from sales of books and other materials [202–205]. Regardless of the origins or current forces driving this anti-vaccine sentiment, the recent experience with deliberate discontinuation or refusal of routine immunization has provided ample forewarning of how this growing multifaceted anti-vaccine movement could reverse decades of progress.

As one reaction to this movement, some clinicians have discontinued or have considered discontinuing their provider relationship with patients who refuse vaccines. However, the American Academy of Pediatrics Committee on Bioethics has advised against this and recommends that clinicians address vaccine refusal by respectfully listening to parental concerns and discussing the risks of non-vaccination to the health of their patients and to the health of their community [195, 206, 207]. While neither confrontation nor rejection is an acceptable response, health professionals must devise effective countermeasures against this emerging challenge to the most fundamental strategy for control of viral infections.

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