Chapter 6

Epidemiology and Control of Viral Diseases

EPIDEMIOLOGY OF VIRAL INFECTIONS

Epidemiology is the study of the determinants, dynamics, and distribution of diseases in populations. Fundamental to the understanding of the occurrence of viral diseases is delineation of the mechanisms whereby viruses are spread and how they cause disease (see Chapter 3: Pathogenesis of Viral Infections and Diseases), how viruses survive in nature, how they evolve and how this potentially alters properties such as virulence, how diseases caused by viruses continue to emerge and reemerge, and how new viral diseases arise, often seemingly from nowhere. The risk of infection and/or disease in an animal or animal population is determined by characteristics of the virus (eg, genetic variation from evolution), the host and host population (eg, passive, innate, and acquired resistance; see Chapter 4: Antiviral Immunity and Virus Vaccines), and behavioral, environmental, and ecological factors that affect virus transmission from one host to another. Epidemiology attempts to meld these factors into a unified, population-based perspective.

Although derived from the root term *demos*, meaning people, the word *epidemiology* is widely used now irrespective of the host; hence, the terms endemic, epidemic, and pandemic are used to describe disease in human, animal, avian, and plant populations. The terms enzootic, epizootic, and panzootic are sometimes used to

describe disease in animal populations, but the distinction as to population type is unnecessary given the same underlying principles and methods of epidemiology. By introducing quantitative measurements of disease trends, epidemiology has come to have a major role in advancing our understanding of the nature of diseases, and in alerting and informing disease control and prevention activities. Epidemiologic study is also effective in clarifying the role of viruses in the etiology of diseases, in understanding the interaction of viruses with environmental determinants of disease, in determining factors affecting host susceptibility, in unraveling modes of transmission, and in large-scale testing of vaccines and drugs.

TERMS AND CONCEPTS USED IN EPIDEMIOLOGY

The term *endemic (enzootic) disease* refers to the presence of several or continuous chains of transmission that result in the continuous occurrence of disease in a population.

Epidemic (epizootic) disease refers to peaks in disease incidence that exceed the endemic baseline or expected incidence of disease. The size of the peak required to categorize a disease as an epidemic or outbreak is arbitrary and is influenced by the background infection rate, the morbidity rate, and the anxiety that the disease arouses because of its clinical severity, economic impact, and zoonotic potential. Thus, a few cases of virulent avian paramyxovirus-1 causing Newcastle disease in a poultry flock might be regarded as an epidemic, whereas a few cases of infectious bronchitis would not.

Pandemic (panzootic) disease refers to a large-scale epidemic involving spread of disease across continents or even worldwide, such as that recently associated with H1N1 influenza virus and, previously, with canine parvovirus, amongst many other examples.

Incubation period refers to the interval between infection and the onset of clinical signs. In many diseases, animals are infectious before they become sick.

Period of contagiousness (infectious period) refers to the time during which an infected animal sheds virus. This period varies depending on the disease concerned. For example, in lentivirus infections such as feline immunodeficiency virus infection, animals shed virus for a very long period before showing clinical signs. In such infections the amount of virus shed may be very small, but because the period of infectivity is so long, the virus is maintained readily in the population.

Seroepidemiology simply denotes the use of serological data as the basis of epidemiological investigation, as determined by diagnostic serological techniques (see Chapter 5: Laboratory Diagnosis of Viral Infections). Seroepidemiology is extremely useful in veterinary disease control activities and in veterinary research. Because of the expense of collecting and storing sera properly, advantage is often taken of a wide range of sources of representative serum samples, such as abattoirs, culling operations (especially useful for assessment of wildlife populations), as well as disease surveillance and vaccination programs. Such sera can be used to determine the prevalence or incidence of particular infections, to evaluate the success of eradication and immunization programs, and to assess the impact, dynamics, and geographic distribution of new, emerging, and reemerging viruses. By detecting antibodies to selected viruses in various age groups of the population, it is possible to determine how effectively viruses have spread or how long it has been since the last appearance of a particular virus in the population. Correlation of serologic data with clinical observations makes it possible to determine the ratio of clinical to subclinical infections.

Molecular epidemiology denotes the use of molecular biological data as the basis of epidemiological investigation (see Chapter 5: Laboratory Diagnosis of Viral Infections). Real time (quantitative) PCR assays and nucleotide sequence data are increasingly used for such studies, as they facilitate rapid detection of viruses and direct genetic comparison of individual virus strains, respectively, as is done in tracking the introduction and relative prevalence of different viral genotypes in animal populations.

COMPUTATIONS AND DATABASES

Calculations of Rates and Proportions

The comparison of disease experience in different populations is expressed in the form of rates and proportions. Multipliers (eg, rates per 10^n) are used to provide rates that are manageable whole numbers—the most common rate multiplier used is 100,000—that is, the given rate is expressed per 100,000 of the given population per unit of time. Four rates or proportions are most widely used to describe disease occurrence in populations: *incidence*, *prevalence*, *morbidity rate*, and *mortality rate*.

The case definition (numerator) is a critical component of rates and proportions that should be standardized to allow comparison of disease occurrence in different populations and subpopulations. Criteria can be specified for confirmed, probable, and possible cases, depending on whether the selected criteria are pathognomonic for the viral disease of interest and whether laboratory results are available for all cases. Different case definitions can be specified at the individual animal and herd or flock levels.

In all four measures (*incidence*, *prevalence*, *morbidity*, and *mortality*), the denominator (total number of animals at risk) may be as general as the total population in a herd, state, or country, or as specific as the population known to be susceptible or at risk (eg, the number of

animals in a specified population that lack antibodies to the virus of interest). In each situation it is imperative that the nature of the denominator is made clear—indeed, epidemiology has been called "the science of the denominator." Each of these measures may be affected by various attributes that distinguish one individual animal from another: age, sex, genetic constitution, immune status, nutrition, pregnancy, and various behavioral parameters. The most widely applicable attribute is age, which may encompass, and can therefore be confounded by, the animal's immune status in addition to various physiologic variables. With the exception of *prevalence* (a proportion) which provides a snapshot of disease at a given time, the other three rates require specification of time, as described in following sections.

Determining the occurrence of a particular disease in a given animal population is more difficult than the computation of the rates described below. The denominator—that is, the number of animals in the population at risk—is often impossible to calculate or estimate accurately, especially in free-ranging wildlife populations. Determining the number of cases of the disease may also prove impossible, depending on the case definition that is selected. Where such information is regarded as essential, government regulations may declare a disease to be *notifiable*, requiring veterinarians to report all cases to authorities. For example, suspicion of the presence of foot-and-mouth disease is notifiable in developed countries.

Incidence

The cumulative incidence, sometimes termed *attack rate* when used during a disease outbreak, is a measure of the occurrence of new cases of infection or disease in a population in a given time period—for example, a month or a year—and is especially useful for describing acute diseases of short duration. For acute infections, several parameters determine the incidence of infection or disease in a population, including: (1) the percentage of susceptible animals; (2) the percentage of susceptible animals that are infected; (3) the percentage of infected animals that suffer disease; and (4) the contact rate for those diseases transmitted by contact, which is affected by animal housing density, housing time, and related factors. The percentage of animals susceptible to a specific virus reflects their past history of exposure to that virus and the duration of their immunity. The percentage infected during a year or a season may vary considerably, depending on factors such as animal numbers and density, season, and—for arbovirus infections—the vector population. Of those infected, only some may develop overt disease; the ratio of clinical to subclinical (inapparent) infections varies greatly between viruses.

The *secondary attack rate*, when applied to comparable, relatively closed groups such as herds or flocks, is a useful measure of the "infectiousness" of viruses transmitted by aerosols or droplets. It is defined as the number of animals in contact with the primary or *index* case(s) that become infected or sick within the maximum incubation period, as a percentage of the total number of susceptible animals exposed to the virus.

Incidence can also be measured as the *incidence density rate*, where the denominator in the incidence calculation is the number of animal years or animal months at risk. This measure is more useful than cumulative incidence for chronic diseases and when populations are open, with many animals leaving and entering.

Prevalence

The incidence of chronic viral disease is often difficult to measure, especially when the onset is insidious and most animals are subclinically infected. For such diseases it is customary to determine the prevalence—that is, the ratio, at a particular point in time, of the number of cases currently present in the population divided by the number of animals in the population; it is a snapshot of the occurrence of infection or disease at a given time and, hence, a proportion rather than a rate. Prevalence is thus a function of the incidence and the duration of the disease.

Seroprevalence relates to the occurrence of antibodies to a particular virus in a population; thus, seroprevalence usually represents the cumulative experience of a population with a given virus, because antibodies often last for many years, or even for life.

Morbidity and Mortality Rates

The morbidity rate is the percentage of animals in a population that develop clinical signs attributable to a particular virus over a defined period of time. Mortality from a disease can be categorized in two ways: the cause-specific mortality rate (the number of deaths from the disease in a given year, divided by the total population at mid-year), often expressed per 100,000 population, or the case-fatality rate (the percentage of animals with a particular disease that die from the disease within a defined time period).

TYPES OF EPIDEMIOLOGIC INVESTIGATION

Conceptual Framework

Case−control, *cohort*, *cross-sectional*, and *long-term herd studies* provide the conceptual frameworks within which the relationships between risk factors and the incidence and prevalence of disease, the safety and efficacy of vaccines, and the therapeutic value of vaccines and drugs can be determined. The latter two relationships can also be assessed with *randomized controlled trials*.

Case−Control Studies

Case−control studies are typically *retrospective*—that is, investigation starts after the disease episode has occurred. In human disease epidemiology, this is the most common type of study, often used to identify risk factors for a disease whose causative agent has not been identified. Advantages of retrospective studies are that they make use of existing data and are relatively inexpensive to carry out. In many instances, they are the only practical method for investigating rare occurrences. Although case−control studies do not require the creation of new data or records, they do require careful selection of the control group, which is sometimes matched to the case (subject) group. The unit of interest might be individual animals or groups of animals such as herds/flocks but, because the necessary records are generally not available in most animal disease outbreaks, this can present irresolvable difficulties in veterinary medicine.

Cohort Studies

Cohort studies are *prospective* or *longitudinal* and involve comparisons of the incidence of disease or infection in risk-factor positive (exposed) and risk-factor negative (control) animals or herds. Examples of risk factors include vaccination history, biosecurity practices, and distance to the neighboring herds. This type of study requires the creation of new data and records. It also requires careful selection of the control group, which should be designed to be as similar as possible to the exposed group, except for the risk factor(s) being studied. Cohort studies do not lend themselves to quick analysis, because groups must be followed until disease is observed, often for long periods of time. This makes such studies expensive. However, when cohort studies are successful, evidence for cause−effect relationships is usually strong.

Cross-Sectional Studies

When risk factors for a specific viral disease are unknown, a cross-sectional study can be carried out relatively quickly using antibody or organism detection methods for the virus and a questionnaire to obtain data on risk factors. Cross-sectional studies provide data on the prevalence of the particular disease/infection in a population in a specific area at a given time, and allow assessment of the relationship between risk factors that don't change over time and of the infection with the virus of interest.

Long-Term Herd Studies

Long-term herd studies, using cross-sectional or longitudinal designs, are another kind of epidemiologic investigation that can provide unique information about the presence and continued activity (or lack of activity) of a given virus in an area. They can also be designed to provide information on the efficacy of vaccines or therapeutic drugs. Despite automation of diagnostic methods and computerization of data files, such studies are still expensive and labor-intensive. When used for evaluating vaccines or therapeutic agents, long-term herd studies have the advantage that they include all the variables attributable to the entire husbandry system.

When used to determine the introduction of a particular virus into a population in a given area, such investigations are referred to as sentinel studies. For example, sentinel studies are widely used for determining the initial introduction of zoonotic arboviruses into high-risk areas—sentinel animals, often chickens, are bled regularly and sera are tested for antibodies or the first evidence of virus activity, so that appropriate vector control actions can be initiated. For animal viruses, other nonavian species are frequently used as sentinels, such as cattle for bluetongue virus infection.

Examples of How Various Kinds of Epidemiological Investigation Are Used in Prevention and Control of Viral Diseases

Investigating Causation of Disease

The original investigations of the production of congenital defects in cattle by Akabane virus provide examples of both case−control and cohort studies. Case−control studies of epidemics of congenital defects in calves, characterized by deformed limbs and abnormal brain development, were carried out in Australia in the 1950s and 1960s, but the cause of the disease was not identified. During the summer and early winter months from 1972 to 1975, more than 40,000 calves were born with these same congenital defects in central and western Japan. Japanese scientists postulated that the disease was infectious, but were unable to isolate a virus from affected calves. However, when precolostral sera from such calves were tested for antibody to a number of viruses, antibody to Akabane virus, a bunyavirus that was first isolated from mosquitoes in Akabane Prefecture in Japan in 1959, was present in almost all sera. A retrospective serologic survey indicated a very strong association between the geographic distribution of the disease and the presence of antibody to the virus, suggesting that Akabane virus was the etiologic agent of the congenital arthrogryposis-hydranencephaly in cattle. Cohort (prospective) studies were then initiated. Sentinel herds were established in Japan and Australia, and it was soon found that the virus could be isolated from fetuses obtained by slaughter or cesarean section for only a short period after infection, thus explaining earlier failures in attempts to isolate virus after calves were born. Experimental inoculation of

pregnant cows with Akabane virus during the first two trimesters resulted in congenital abnormalities in calves similar to those seen in natural cases of the disease; clinical signs were not seen in cows. Following these studies and estimates of the economic impact of the disease, a vaccine was developed and ongoing control programs were started.

In contrast to the considerable time required to establish Akabane virus to be the causative agent of distinctive congenital defects amongst cattle in Japan and Australia, in 2011 another but previously unrecognized orthobunyavirus was quickly identified as the cause of a similar disease syndrome among livestock in northern Europe. This disease syndrome was first recognized among adult dairy cattle in Germany and the Netherlands, and a few months later by the birth of calves and lambs with congenital arthrogryposis and hydranencephaly identical to those caused by Akabane virus. Schmallenberg virus—named after the town in Germany where the syndrome was first recognized in 2011—was characterized by metagenomic methods within days of recognition of the disease, even before it was isolated in cell culture.

Investigating Geographical Distribution and Genetic Variation of Viruses

The global epidemiology of bluetongue virus infection was defined using cross-sectional and long-term herd studies, and the application of both seroepidemiology and molecular epidemiology. Bluetongue virus is endemic throughout tropical and temperate regions of the world, but before 1998 the virus had only transiently occurred in Europe. Since 1998, several serotypes and multiple different strains of bluetongue virus have spread throughout extensive portions of Europe, precipitating a massive disease epidemic, predominantly in sheep but also in cattle. The extensive use of long-term sentinel herd studies coupled with entomological surveillance in several European countries, notably Italy, has definitively established the distribution of the virus and important aspects of its transmission cycle. Furthermore, molecular analyses of the virus serotypes and strains that invaded Europe have led, in some instances, to determination of their precise geographic origin by comparison with bluetongue viruses isolated elsewhere in the world. Molecular techniques have also been used to monitor the evolution of the viruses within each region, and to determine the contribution of live-attenuated vaccine viruses to the evolution of field strains of the virus. International trade regulations have been substantially modified to reflect the findings from these studies and data from similar studies in other regions of the world such as North America, Australia, and Southeast Asia, where bluetongue virus infection of ruminants is also endemic but disease is typically sporadic or rare.

Vaccine Trials

The immunogenicity, potency, safety, and efficacy of vaccines are first studied in laboratory animals, followed by small-scale, closed trials in the target animal species and, finally, by large-scale field trials. In the latter, epidemiologic methods like those employed in cohort studies are used. There is no alternative way to evaluate new vaccines, and the design of randomized controlled field trials has now been developed so that they yield maximum information with minimum risk and cost. Even with this system, however, a serious problem may be recognized only after a vaccine has been licensed for commercial use. This occurred, for example, after the introduction of live-attenuated virus vaccines for infectious bovine rhinotracheitis (caused by bovine herpesvirus 1) in the United States in the 1950s. Surprisingly, the vaccines had been in use for 5 years before it was recognized that abortion was a common sequel to vaccination. Case−control and cohort studies confirmed the causal relationship.

Mathematical Modeling

From the time of William Farr, who studied both medical and veterinary problems in the 1840s, mathematicians have been interested in "epidemic curves" and secular trends in the incidence of infectious diseases. With the development of mathematical modeling using the computer, there has been a resurgence of interest in the dynamics of infectious diseases within populations. Because modeling involves predictions about future occurrences of diseases, models carry a degree of uncertainty; skeptics have said that "for every model there is an equal and opposite model," but in recent years models have played an increasingly important role in directing disease control activities.

Mathematical models have been developed to predict various epidemiologic parameters, such as (1) critical population sizes required to support the continuous transmission of animal viruses with short and long incubation periods; (2) the dynamics of endemnicity of viruses that establish persistent infections; and (3) the important variables in age-dependent viral pathogenicity. Computer modeling also provides insights into the effectiveness of disease control programs. Models bring a number of issues into focus, and the results are often unexpected, pointing to the need for better data and different control strategies especially for potential national and international spread of exotic viral diseases. Models are also dependent on detailed information on the mechanisms of virus transmission and virus survival in nature, as is discussed in the next section.

VIRUS TRANSMISSION

Viruses survive in nature only if they can be transmitted from one host to another, whether of the same or different

species. Transmission cycles require virus entry into the body, replication, and shedding, with subsequent spread to another host (see Chapter 3: Pathogenesis of Viral Infections and Diseases). Aspects relevant to the spread of viruses in populations are covered here.

Virus transmission may be *horizontal* or *vertical*. Vertical transmission describes transmission from dam to offspring. However, most transmission is horizontal—that is, between animals within the population at risk, and can occur via direct contact, indirect contact, or by a common vehicle; they may be air-borne, vector-borne, or iatrogenic. Some viruses are transmitted in nature via several modes, others exclusively by a single mode.

Horizontal Transmission

Direct-Contact Transmission

Direct-contact transmission involves actual physical contact (eg, licking, rubbing, or biting) between an infected animal and a susceptible animal. This category also includes sexual contact, which, for example, is important in the transmission of some herpesviruses and retroviruses such as human immunodeficiency virus (HIV).

Indirect-Contact Transmission

Indirect-contact transmission occurs via *fomites*, such as shared eating containers, bedding, dander, restraint devices, vehicles, clothing, improperly sterilized surgical equipment, or improperly sterilized syringes or needles (the latter also comes under the heading of iatrogenic transmission). For example, equine arteritis virus that is shed in the semen of carrier stallions can be spread on fomites or contaminated bedding to cohoused horses without any direct sexual contact.

Common-Vehicle Transmission

Common-vehicle transmission includes fecal contamination of food and water supplies (fecal−oral transmission) and virus-contaminated meat or bone products [eg, for the transmission of classical swine fever (hog cholera) and bovine spongiform encephalopathy].

Air-Borne Transmission

Air-borne transmission, which results in infection of the respiratory tract, occurs via droplets and droplet nuclei (aerosols) emitted from infected animals during coughing or sneezing (eg, influenza) or from environmental sources such as dander or dust from bedding (eg, Marek's disease). Large droplets settle quickly, but microdroplets evaporate, forming droplet nuclei (less than 5 μm in diameter) that remain suspended in the air for extended periods. Droplets may travel only a meter or so, but droplet nuclei may travel long distances—many kilometers if wind and other weather conditions are favorable. In aquatic animals, waterborne transmission is the analogous mode of transmission for viruses (eg, infectious salmon anemia).

Arthropod-Borne Transmission

Arthropod-borne transmission involves the bites of arthropod vectors (eg, mosquitoes transmit equine encephalitis viruses; ticks transmit African swine fever virus; and *Culicoides* spp. transmit bluetongue and African horse sickness viruses) (see "Arthropod-Borne Virus Transmission Patterns" section).

Iatrogenic Transmission

Iatrogenic ("caused by the doctor") transmission occurs as a direct result of some activity of the attending veterinarian, veterinary technologist, or other person in the course of caring for animals, usually via nonsterile equipment, multiple-use syringes, or inadequate hand washing. Iatrogenic transmission has been important in the spread of equine infectious anemia virus via multiple-use syringes and needles. Similarly, chickens have been infected with reticuloendotheliosis virus via contaminated Marek's disease vaccine.

Nosocomial Transmission

Nosocomial transmission occurs while an animal is in a veterinary hospital or clinic. During the peak of the canine parvovirus epidemic in the 1980s, many puppies became infected in veterinary hospitals and clinics. In some hospitals, the disinfectants in routine use were found to be ineffective against the virus. Feline and canine respiratory and enteric viral infections are also acquired nosocomially with considerable frequency in animal shelters. In human medicine, the recent Ebola virus epidemic in West Africa has graphically illustrated the potential significance of iatrogenic nosocomial infection, and the associated threat to healthcare workers.

Zoonotic Transmission

Because most viruses are host-restricted, the majority of virus infections are maintained in nature within populations of the same or closely related species. However, a number of viruses are spread naturally between several different species of animals—for example, rabies and the arboviral encephalitides. The term *zoonosis* is used to describe infections that are transmissible from animals to humans, or the reverse (also termed *zooanthroponosis*). Zoonoses, whether involving domestic or wild animal reservoirs, usually occur only under conditions in which humans are engaged in activities involving close contact with animals, or where viruses are transmitted by arthropods.

Vertical Transmission

The term "vertical transmission" is usually used to describe infection that is transferred from dam to embryo, or fetus, or newborn before, during, or shortly after parturition, although some authorities prefer to restrict the term to situations in which infection occurs before birth. Certain retroviruses are transmitted vertically via the integration of proviral DNA directly into the DNA of the germ line of the fertilized egg. Cytomegaloviruses are often transmitted to the fetus via the placenta, whereas other herpesviruses are transmitted during passage through the birth canal. Yet other viruses are transmitted via colostrum and milk (eg, caprine arthritis-encephalitis virus and maedi-visna virus of sheep), or eggs (eg, chicken infectious anemia virus). Vertical transmission of a virus may cause early embryonic death or abortion (eg, several lentiviruses) or may be associated with congenital disease (eg, bovine viral diarrhea virus, border disease virus, porcine enterovirus), or the infection may be the cause of congenital defects (eg, Akabane, Cache Valley and Schmallenberg viruses, bluetongue virus, feline parvovirus).

MECHANISMS OF SURVIVAL OF VIRUSES IN NATURE

Perpetuation of a virus in nature depends on the maintenance of serial infections—that is, a chain of transmission; the occurrence of disease is neither required nor necessarily advantageous. Indeed, although clinical cases may be somewhat more productive sources of virus than inapparent infections, the latter are generally more numerous and more important, because they do not restrict the movement of infectious individuals and thus provide a better opportunity for virus dissemination. As our knowledge of the different features of the pathogenesis, species susceptibility, routes of transmission, and environmental stability of various viruses has increased, epidemiologists have recognized four major patterns by which viruses maintain serial transmission in their host(s): (1) the acute self-limiting infection pattern, in which transmission is always affected by host population size; (2) the persistent infection pattern; (3) the vertical transmission pattern; and (4) the arthropod-borne virus transmission pattern.

The physical stability of a virus affects its survival in the environment; in general, viruses that are transmitted by the respiratory route have low environmental stability, whereas those transmitted by the fecal−oral route have a higher stability. Thus, stability of the virus in water, on fomites, or on the mouthparts of mechanical arthropod vectors, favors transmission. This is particularly important in small or dispersed animal communities; for example, the parapox virus that causes orf in sheep survives for months in pastures. During the winter, myxoma virus, which causes myxomatosis in rabbits, can survive for several weeks on the mouthparts of mosquitoes.

Most viruses have a principal mechanism for survival, but if this mechanism is interrupted—for example, by a sudden decline in the population of the host species—a second or even a third mechanism may exist as a "backup." In bovine viral diarrhea there is a primary, direct animal-to-animal transmission cycle; however, long-term infection in herds is maintained by the less common, persistent shedding of virus by congenitally infected cattle. An understanding of these mechanisms for virus perpetuation is valuable in designing and implementing control programs.

Acute Self-Limiting Infection Patterns

The most precise data on the importance of population size in acute, self-limiting infections has come historically from studies of measles, which is a cosmopolitan human disease. Measles has long been a favorite disease for modeling epidemics, because it is one of the few common human diseases in which subclinical infections are rare, clinical diagnosis is straightforward, and postinfection immunity is life-long. Measles virus is related closely to canine distemper virus, and many aspects of the model apply equally well to it and other morbilliviruses (see Chapter 17: *Paramyxoviridae* and *Pneumoviridae*). Survival of measles virus in a population requires a large continuous supply of susceptible hosts. Analyses of the incidence of measles in large cities and in island communities have shown that a population of about half a million persons is needed to ensure a large enough annual input of new susceptible hosts, by birth or immigration, to maintain the virus in the population. Because infection depends on respiratory transmission, the duration of epidemics of measles is correlated inversely with population density. If a population is dispersed over a large area, the rate of spread is reduced and the epidemic will last longer, so that the number of susceptible persons needed to maintain the transmission chain is reduced. However, in such a situation a break in the transmission chain is much more likely. When a large percentage of the population is susceptible initially, the intensity of the epidemic builds up very quickly and attack rates are almost 100% (*virgin-soil epidemic*). There are many examples of similar transmission patterns among viruses of domestic animals, but quantitative data are not as complete as those for measles. *Exotic viruses* (syn., foreign animal viral diseases)—that is, those that are not present in a particular country or region—represent the most important group of viruses with a potential for causing virgin-soil epidemics, as graphically illustrated recently with the bluetongue and Schmallenberg virus epidemics in Europe, and porcine epidemic diarrhea virus among swine in North America.

The history of rinderpest in cattle in Africa, in the early 20th century, shows many parallels with measles in isolated human populations. When it was first introduced into cattle populations the initial impact was devastating. Cattle and wild ruminants of all ages were susceptible, and the mortality was so high that in Tanzania the ground was so littered with the carcasses of cattle that a Masai tribesman commented that "the vultures had forgotten how to fly." The development of vaccines, beginning in the 1920s, changed the epidemiology of rinderpest, leading to a period in the 1960s when its global eradication was anticipated. Unfortunately, in the 1970s, vaccination programs in West Africa were maintained poorly and by the 1980s the disease had once again become rampant and the cause of major losses of livestock in many parts of Africa. This prompted renewed vaccination and control campaigns in Africa and the Indian subcontinent and, ultimately, set the stage for rinderpest's global eradication in 2011.

The cyclical nature of the occurrence of such diseases is determined by several variables, including the rate of build-up of susceptible animals, introduction of the virus, and environmental conditions that promote virus spread.

Persistent Infection Patterns

Persistent viral infections, whether they are associated with acute initial disease or with recurrent episodes of clinical disease, play an important role in the perpetuation of many viruses. For example, recurrent virus shedding by a persistently infected animal can reintroduce a virus into a population of susceptible animals, all of which have been born since the last clinically apparent episode of infection. This transmission pattern is potentially important for the survival of bovine viral diarrhea virus, classical swine fever (hog cholera) virus, and some herpesviruses, and such viruses have a much smaller critical population size than occurs in acute self-limited infections. Indeed, the sustaining population for some herpesviruses may be as small as a single farm, kennel, cattery, or breeding unit.

Sometimes the persistence of infection, the production of disease, and the transmission of virus are dissociated; for example, togavirus and arenavirus infections have minimal adverse effect on their reservoir hosts (arthropods, birds, and rodents) but transmission is very efficient. In contrast, the persistence of infection in the central nervous system, as with canine distemper virus, is of no epidemiologic significance, as no infectious virus is shed from this site. Infection of the central nervous system may have a severe effect on the dog, but is of no consequence for survival of the virus.

Vertical Transmission Patterns

Transmission of virus from the dam to the embryo, fetus, or newborn can be important in virus survival in nature:

all arenaviruses, several herpesviruses, parvoviruses, pestiviruses, and retroviruses, some togaviruses, and a few bunyaviruses and coronaviruses may be transmitted in this way. Indeed, if the consequence of vertical transmission is life-long persistent infection, as in the case of arenaviruses and retroviruses, the long-term survival of the virus is assured. Virus transmission in the immediate perinatal period, by contact or via colostrum and milk, is also important.

Arthropod-Borne Virus Transmission Patterns

Several arthropod-borne diseases are discussed in appropriate chapters of Part II of this book; this chapter considers some common features that will be useful in understanding their epidemiology and control. A vast number of arboviruses have been described—increasingly by metagenomic analyses—of which some 40 cause disease in domestic animals, and many of these also cause zoonotic diseases (Table 6.1). Sometimes arthropod transmission may be mechanical, as in myxomatosis and fowlpox, in which mosquitoes act as "flying needles." More commonly, transmission involves replication of the virus in the arthropod vector, which may be a tick, a mosquito, a sandfly (*Phlebotomus* spp.), or a midge (*Culicoides* spp.).

The arthropod vector acquires virus by feeding on the blood of a viremic animal. Replication of the ingested virus, initially in the insect gut, and its spread to the salivary gland take several days (the *extrinsic incubation period*); the interval varies with different viruses and is influenced by ambient temperature. Virions in the salivary secretions of the vector are injected into new animal hosts during blood meals. Arthropod transmission provides a way for a virus to cross species barriers, as the same arthropod may bite birds, reptiles, or mammals that rarely or never come into close contact.

Most arboviruses have localized natural habitats in which specific receptive arthropod and vertebrate hosts are involved in the virus' life cycle. Vertebrate reservoir hosts are usually wild mammals or birds; domestic animals and humans are rarely involved in primary transmission cycles, although the exceptions to this generalization are important (eg, Venezuelan equine encephalitis virus in horses, yellow fever and dengue viruses in humans). Domestic animal species are, in most cases, infected incidentally—for example, by the geographic extension of a reservoir vertebrate host and/or a vector arthropod.

Most arboviruses that cause periodic epidemics have ecologically complex endemic cycles, which often involve arthropod and vertebrate hosts that are different from those involved in epidemic cycles. Endemic cycles, which are often poorly understood and inaccessible to

TABLE 6.1 Examples of Important New, Emerging, and Reemerging Zoonotic Viruses

Bovine spongiform encephalopathy prion; first recognized in cattle 1986 and later as the cause of human central nervous system disease: new-variant Creutzfeldt–Jakob disease

Crimean-Congo hemorrhagic fever virus[a] (tick borne); reservoir in sheep; severe human disease with 10% mortality; widespread across Africa, the Middle East, and Asia

Eastern equine encephalitis virus; increase in number of human cases in eastern United States, in areas where it was rarely detected previously

Ebola[a] and Marburg[a] viruses (bats and nonhuman primates appear to be natural reservoir hosts; Ebola and Marburg viruses are the causes of the most lethal hemorrhagic fevers known). The largest outbreak of human Ebola infection occurred in western Africa in 2014 and is ongoing

Hendra virus; first recognized in Queensland, Australia, in 1994; the cause of fatal acute respiratory distress syndrome in horses; spread to humans causing similar, also fatal, disease; bats serve as reservoir host; Nipah causes a similar zoonotic disease in humans in Malaysia, but with pigs as the amplifying animal reservoir host

Guanarito virus[a] (rodent borne); the cause of Venezuelan hemorrhagic fever

Hantaviruses[a] (rodent borne); the cause of important rodent-borne hemorrhagic fever in Asia and Europe; Sin Nombre virus and related viruses are the cause of hantavirus pulmonary syndrome in the Americas

Influenza viruses (reservoir in birds, especially waterfowl birds, sometimes with intermediate evolution in swine, and virus species jumping, bringing new viruses to human populations each year; the cause of the single most deadly human epidemic ever recorded—the pandemic of 1918 in which 25–40 million people died; ongoing episodes globally

Japanese encephalitis virus (mosquito borne); swine serve as amplifying reservoir hosts; severe, lethal encephalitis in humans; spread recently across southeast Asia; great epidemic potential

Junin virus[a] (rodent borne); the cause of Argentine hemorrhagic fever

Lassa virus[a] (rodent borne); an important and severe disease in West Africa

Machupo virus[a] (rodent borne); the cause of Bolivian hemorrhagic fever

Rabies virus (transmitted by the bite of rabid animals); raccoon epidemic still spreading across the northeastern United States; thousands of deaths every year in India, Sri Lanka, the Philippines, and elsewhere

Rift Valley fever virus[a] (mosquito borne); sheep, cattle, and wild mammals serve as amplifying hosts; the cause of one of the most explosive epidemics ever seen when the virus first appeared in 1977 in Egypt; subsequent epidemics in southern and eastern Africa, and the Arabian Peninsula

Ross River virus (mosquito borne); cause of human epidemic arthritis; has moved across the Pacific region several times. A potential cause of systemic disease in horses as well as humans

Sabiá virus[a] (rodent borne); cause of severe, even fatal, hemorrhagic fever in Brazil

Severe acute respiratory disease syndrome (SARS) coronavirus (reservoir in bats, spread to humans by palm civets, raccoon dogs, etc. in live animal markets in Asia; severe respiratory disease in affected humans; Middle East respiratory syndrome (MERS) is caused by a related coronavirus first identified in humans in 2012, virus is spread from camels, with bats likely to be the reservoir host; MERS coronavirus spreads between humans, large outbreak of human disease with high case-fatality rate in South Korea in 2015

Vaccinia virus infections of humans working with cattle in Brazil—possible resurgence of virus in human population no longer vaccinated for smallpox

Yellow fever virus[a] (mosquito borne); monkeys serve as reservoir hosts; one of the most deadly diseases in history, potential for urban reemergence

[a]Viruses that cause hemorrhagic fevers in humans.

effective control measures, provide for the amplification of virus and, therefore, are critical in dictating the magnitude of epidemics.

When arthropods are active, arboviruses replicate alternately in vertebrate and invertebrate hosts. A puzzle that has concerned many investigators has been to understand what happens to these viruses during the winter months in temperate climates when the arthropod vectors are inactive. Two important mechanisms for "overwintering" are *transovarial* and *trans-stadial transmission*. Transovarial transmission occurs with the tick-borne flaviviruses, and has been shown to occur with some mosquito-borne bunyaviruses and flaviviruses. Some bunyaviruses are found in high northern latitudes where

the mosquito breeding season is too short to allow virus survival by horizontal transmission cycles alone; many of the first mosquitoes to emerge each summer carry virus as a result of transovarial and trans-stadial transmission, and the pool of virus is amplified rapidly by horizontal transmission in mosquito−vertebrate−mosquito cycles.

Vertical transmission in arthropods may not explain overwintering of all arboviruses, but other possibilities are still unsubstantiated or speculative. For example, hibernating vertebrates have been thought to play a role in overwintering of certain arboviruses. In cold climates, bats and some small rodents, as well as snakes and frogs, hibernate during the winter months. Their low body temperatures have been thought to favor persistent infection of certain viruses, with recrudescent viremia occurring when the temperature increases in the spring. Although demonstrated in the laboratory, this mechanism has never been shown to occur in nature. Similarly, in temperate climates, individual insects can survive for extended periods during the winter months and initiate a low-level cycle of vertebrate−invertebrate virus transmission that sustains viruses during the interseasonal transmission period—as identified recently as an overwintering mechanism of bluetongue virus in California.

Many human activities disturb the natural ecology and, hence, the natural arbovirus life cycles, and these activities have been incriminated in the geographic spread or increased prevalence of diseases caused by these viruses:

1. Population movements and the intrusion of humans and domestic animals into new arthropod habitats have resulted in dramatic epidemics. Some have had historic impact: the Louisiana Purchase came about because of the losses Napoleon's army experienced from yellow fever in the Caribbean. Several decades later, the same disease markedly and adversely affected the building of the Panama Canal. Ecologic factors pertaining to unique environments and geographic factors have contributed to many new, emergent disease episodes. Remote econiches, such as islands, free of particular species of reservoir hosts and vectors, are often particularly vulnerable to an introduced virus.

2. Deforestation has been the key to the exposure of farmers and domestic animals to new arthropods—there are many contemporary examples of the importance of this kind of ecological disruption. Deforestation has also been associated with the increased emergence of certain filo- and arenaviruses.

3. Increased long-distance travel facilitates the carriage of exotic arthropod vectors around the world. The carriage of the eggs of the Asian mosquito, *Aedes albopictus*, to the United States in used tires represents an unsolved problem of this kind. The increased long--distance transportation of livestock facilitates the carriage of viruses and arthropods (especially ticks) around the world.

4. Ecologic factors pertaining to water usage—that is, increasing irrigation and the expanding reuse of water, are becoming very important factors in the emergence of viral disease. The problem with primitive water and irrigation systems, which are developed without attention to arthropod control, is exemplified in the emergence of Japanese encephalitis into new areas of Southeast Asia.

5. New routes of long-distance bird migrations, brought about by new man-made water impoundments, represent an important yet still unverified risk of introduction of arboviruses into previously noninfected areas. The extension of the geographical range of Japanese encephalitis virus into new areas of Asia has probably involved virus carriage by birds.

6. Ecologic factors pertaining to environmental pollution and uncontrolled urbanization are contributing to many new, emergent disease episodes. Arthropod vectors breeding in accumulations of water (tin cans, old tires, etc.) and sewage-laden water are a worldwide problem. Environmental chemical toxicants (herbicides, pesticides, and residues) can also affect vector−virus relationships directly or indirectly, including fostering the development of mosquito resistance to licensed insecticides.

7. Climate change, which affects sea levels, estuarine wetlands, fresh water swamps, and human habitation patterns, may be affecting vector−virus relationships throughout the tropics; however, definitive data are lacking and many programs to study the effects of global warming on emergence of infectious diseases have failed to adequately address the potential importance of other environmental and anthropogenic factors in the process.

The history of the European colonization of Africa is replete with examples of new arbovirus diseases resulting from the introduction of susceptible European livestock into that continent—for example, African swine fever, African horse sickness, Rift Valley fever, Nairobi sheep disease, and bluetongue. The viruses that cause these diseases are now feared in many industrialized countries as exotic threats that may devastate their livestock, with recent poignant examples of events such as the emergence of bluetongue throughout Europe. Another example of the importance of ecologic factors is infection of horses in the eastern part of North America with eastern equine encephalitis virus, when their pasturage overlaps with the swamp-based habitat of the mosquito−bird−mosquito cycle of this virus. Similarly, in Japan and south-eastern Asian countries, swine may become infected with Japanese encephalitis virus and become important amplifying hosts when they are bitten by mosquitoes that breed in rice fields.

Tick-borne flaviviruses illustrate two features of epidemiologic importance. First, transovarial infection in ticks is often sufficient to ensure survival of the virus independently of a cycle in vertebrates; vertebrate infection amplifies the population of infected ticks. Second, for some of these viruses, transmission from one vertebrate host to another, once initiated by the bite of an infected tick, can also occur by mechanisms not involving an arthropod. Thus, in central Europe and the eastern part of Russia, a variety of small rodents may be infected with tick-borne encephalitis viruses. Goats, cows, and sheep are incidental hosts and sustain inapparent infections, but they excrete virus in their milk. Adult and juvenile ungulates may acquire virus during grazing on tick-infested pastures, and newborn animals may be infected by drinking infected milk. Humans may be infected by a tick bite or by drinking milk from an infected goat. Similarly, African swine fever has spread recently by aerosol infection of swine throughout an extensive area of Eurasia without requirement for the ticks that are essential vectors of the virus in historically endemic regions of Africa.

Variations in Disease Incidence Associated with Seasons and Animal Management Practices

Many viral infections show pronounced seasonal variations in incidence. In temperate climates, arbovirus infections transmitted by mosquitoes, hematophagous midges, or sandflies occur mainly during late summer and early fall, when vectors are most numerous and active. Infections transmitted by ticks occur most commonly during the spring and early summer months. Other biologic reasons for seasonal disease occurrence include both virus and host factors. Influenza viruses and poxviruses survive better in air at low humidity than high, and all viruses survive better at lower temperatures in aerosols. It has also been suggested that there are seasonal changes in the susceptibility of the host, perhaps associated with changes in the physiological status of nasal and oropharyngeal mucous membranes.

With the exception of arboviral diseases, more important in veterinary medicine than any natural seasonal effects are the changes in housing and management practices that occur in different seasons. Housing animals such as cattle and sheep for the winter often increases the incidence of respiratory and enteric diseases. These diseases often have a complex pathogenesis with an obscure primary etiology, usually viral, followed by secondary infections with other pathogens, often bacteria. In such cases, diagnosis, prevention, and treatment of infectious diseases must be integrated into an overall system for the management of facilities as well as husbandry practices. In areas where animals are moved—for example, to feedlots or seasonally to distant pasturage—there are two major problems: animals are subjected to the stress of transportation, and they are brought into contact with new populations that may be carrying and shedding different infectious agents.

In areas of the world where livestock are moved annually over vast distances, such as in the Sahel zone of Africa, viral diseases such as pestes des petits ruminants are associated with contact between previously separate populations brought about by this traditional husbandry practice. In southern Africa, the communal use of waterholes during the dry season promotes the exchange of viruses such as foot-and-mouth disease virus between different species of wildlife and, potentially, between wildlife and domestic animals.

Epidemiologic Aspects of Immunity

Immunity acquired from prior infection or from vaccination plays a vital role in the epidemiology of viral diseases; in fact, vaccination (see Chapter 4: Antiviral Immunity and Virus Vaccines) is the single most effective method of controlling most viral diseases. For example, vaccination against canine distemper and infectious canine hepatitis has sharply decreased the incidence of both diseases amongst pet dogs in many countries. For some viruses, immunity is relatively ineffective because of the lack of neutralizing of antibodies at the site of infection (eg, the respiratory or intestinal tract). Respiratory syncytial viruses cause mild to severe respiratory tract disease in cattle and sheep. Infections usually occur during the winter months when the animals are housed in confined conditions. The virus spreads rapidly by aerosol infection, and reinfection of the respiratory tract is not uncommon. Pre-existing antibody, whether derived passively by maternal transfer or actively by prior infection, does not prevent virus replication and excretion, although clinical signs are usually mild when the antibody titer is high. Not surprisingly, vaccination is not always effective.

EMERGING VIRAL DISEASES

An emerging viral disease is one that is newly recognized or newly evolved, or that has occurred previously but shows an increase in incidence or expansion in geographical, host, or vector range. By this definition, numerous viral diseases in this book currently qualify as emerging diseases. Tables 6.1 and 6.2 list some of these diseases and the viruses that cause them. Constant changes in demographic, ecological, and anthropogenic factors ensure that new and recurring diseases will continue to emerge, but virological and host determinants also contribute to the emergence of some viral diseases, and the emergence of new diseases in particular.

TABLE 6.2 Examples of Important New, Emerging, and Reemerging Animal Viruses

African horse sickness virus (vector *Culicoides* spp.); endemic in sub-Saharan Africa and has incurred on occasion into the Iberian Peninsula, the Middle East and Asian subcontinent; recently active in Ethiopia and West Africa; a major threat to horses worldwide

African swine fever virus (tick borne) and also spread by direct contact; an extremely pathogenic virus; recently present in Russia, Georgia, and portions of eastern Europe and the Baltic countries; a potential threat to commercial swine industries worldwide

Astrovirus confirmed as the cause of sporadic encephalitis of cattle, and neurologic disease in other species

Avian influenza viruses; highly pathogenic avian influenza viruses in Asia, Africa, Europe, and North America; major threat to commercial poultry industries of all countries

Bluetongue virus (vector *Culicoides* spp); major epidemics in Europe forced revision of European Union and OIE trade/animal movement protocols; live-attenuated vaccine virus strain has recently circulated in Russia and eastern Europe

Bovine spongiform encephalopathy; a prion disease that remains a barrier to international livestock trade, and a threat to cattle and human health

Canine influenza virus; H3N8 equine influenza virus that was identified in greyhound dogs in Florida in 2004, and H3N2 avian virus that entered the dog population of Asia in 2004. Can cause fatal hemorrhagic pneumonia; both viruses now circulate in dogs in the United States

Epizootic hemorrhagic disease virus (vector *Culicoides* spp.); in cattle in the Mediterranean Basin, Madagascar, South Africa, and North America

Equine coronavirus; increasingly recognized as an important cause of disease in adult horses

Equine pegivirus (related to human hepatitis C virus, family *Flaviridae*) recently identified as a persistent infection in clinically normal horses

Feline calicivirus; a variant feline calicivirus is associated with a highly virulent systemic infection of cats

Foot-and-mouth disease is considered the most dangerous viral disease of animals in the world today because of its capacity for rapid transmission and great economic loss; still entrenched in Africa, the Middle East, and Asia; still capable of emergence in any commercial cattle or swine industry: outbreaks most recently in the Far East (Japan, Taiwan, and South Korea)

Infectious salmon anemia virus (ISAV) infection is a major production limiting disease in Atlantic salmon worldwide There are 2 strain types: highly polymorphic region (HPR)-deleted (virulent) or HPR0 (nonvirulent ISAV with a nondeleted HPR). HPR0 may revert to virulent (HPR-deleted) strains

Ostreid herpesvirus 1 microvariants cause mortality in Pacific Oysters and have spread worldwide in the last decade

Porcine circovirus 2, now recognized as a cofactor in several important disease syndromes of swine worldwide

Porcine delta coronavirus and Porcine epidemic diarrhea virus; coronaviruses that cause a transmissible gastroenteritis-like disease with high fatality rates in susceptible swine; spread recently throughout North America

Proventricular dilation disease of psittacine birds caused by a bornavirus distinct from mammalian bornaviruses

Salmon alphavirus Infection may cause pancreas disease (syn. sleeping disease) in Atlantic salmon and trout. The infection was recently listed by OIE recognizing its global importance to trade

Schmallenberg virus, an orthobunyavirus, was first detected in Germany in 2011, where it caused congenital malformations in cattle, sheep, and goats similar to those associated with Akabane and Cache Valley virus infections. It is has since been detected in many European countries

West Nile virus, the cause of neurological disease in horses and high mortality in birds in North America and portions of Europe; emergence and recognition of virulent lineage 2 viruses

VIROLOGICAL DETERMINANTS OF THE EMERGENCE OF VIRAL DISEASES

Viruses exist, not as individuals of a single genotype, but rather as populations of genetically distinct but related strains. The number of individual virus species continues to grow, particularly with the evaluation of wildlife and other "nontraditional" species such as reptiles and fish. With the advent of molecular technologies and metagenomic analyses, the numbers of distinct virus strains within individual virus species continues to grow even more rapidly—it has been estimated that there may be several hundred thousand mammalian viruses in total. The importance of this genetic diversity is that new viruses will continue to emerge, potentially to cause disease in animals and humans. Furthermore, specific strains of the same virus species can have profoundly different biological properties, including such critical determinants as host range, tissue tropism, and virulence. Thus, new diseases continue to emerge as a consequence of evolution of novel viruses that arise from

endemic viruses. An appreciation of viral genetics and evolution, therefore, is central to the understanding of the emergence of viral diseases.

In nature, viruses have an ongoing series of replication cycles as they are transmitted from host to host. During this process, genetic variants are continually generated, some of which will have different biological properties (such as virulence, tropism, or host range) than the parent virus from which they arise. Many viruses, particularly RNA viruses, have short generation times and high mutation rates, whereas other viruses evolve through more drastic genetic changes, including the exchange of entire gene segments (reassortment), gene deletion or acquisition, recombination, and translocation. Selective pressures exerted by their animal hosts or insect vectors can favor the selection of certain of these biological variants, primarily because of their preferential ability to be transmitted serially. Properties important in the survival and evolutionary progression of viruses in nature can include:

1. *The capacity to replicate rapidly.* In many instances, the most virulent strains of a virus replicate faster than more temperate strains. However, if replication is too rapid, it can be self-defeating—extremely rapid viral growth may not allow time enough for transmission before the host is removed by death or severe illness.

2. *The capacity to replicate to high titer.* Arthropod-borne viruses develop a very high viremia titer in vertebrate hosts as a survival mechanism to favor infection of the next arthropod. The same viruses also produce especially high titers in the salivary glands of their arthropod hosts in order to favor infection of the next vertebrate host. Such high virus titers can be associated with silent infections in some natural vertebrate hosts (eg, reservoir avian hosts), but usually in other vertebrate hosts the evolution of this capacity is most often associated with severe, even fatal, illness.

3. *The capacity to replicate in certain key tissues.* This quality is often important for the completion of the virus transmission cycle. For example, the evolution of virus tropisms and the employment of specific host-cell receptors define many disease patterns. Further, the evolution of the capacity to grow in immunologically sequestered sites or in cells of the immune system itself provides a great survival advantage (see Chapter 3: Pathogenesis of Viral Infections and Diseases).

4. *The capacity to be shed for long periods of time.* The evolution of the capacity for chronic shedding offers exceptional opportunity for virus survival and entrenchment. Recrudescence and intermittent shedding add additional survival advantages to the virus (eg, herpesvirus infections in all animals).

5. *The capacity to elude host defenses.* Animals have evolved elaborate immune systems to defend themselves against viruses, but viruses, in turn, have evolved equally elaborate systems to evade host defenses (see Chapter 4: Antiviral Immunity and Virus Vaccines). Viruses, particularly those with large genomes, have genes that encode proteins that interfere with specific host antiviral activities. The capacity to cause fetal infection and persistent postnatal viral infection represents an evolutionary progression that gives the virus an extreme survival advantage (eg, bovine viral diarrhea virus infection in calves, or lymphocytic choriomeningitis virus infection in mice).

6. *The capacity to survive after being shed into the external environment.* All things being equal, a virus that has evolved a capsid that is environmentally stable has an evolutionary advantage. For example, because of its stability, canine parvovirus was transported around the world within 2 years of its emergence, mostly by carriage on fomites (human shoes and clothing, cages, etc.).

7. *The capacity to be transmitted vertically.* Viruses that employ vertical transmission and survive without ever confronting the external environment represent yet another evolutionary progression.

Evolution of Viruses and Emergence of Genetic Variants

A simple question that can be posed is: "how important is genetic diversity to the survival of viruses?" Predictably, the answer is not straightforward. Viruses that cause sudden epidemics of disease, such as outbreaks of foot-and-mouth disease, influenza, and severe acute respiratory syndrome (SARS), frequently attract great public interest and concern. It is to be stressed, however, that these viruses emerge from some endemic niche, and it is clear that, as a group, those viruses that are constantly present in populations (endemic) often exact a greater ongoing toll than emerging or new diseases. Thus, an understanding of virus evolution is prerequisite to the understanding of both emergence of viral diseases and the maintenance of endemic ones.

Viruses have evolved with variable reliance on the generation of genetic diversity. Morbilliviruses like rinderpest, measles, and canine distemper have limited genetic and antigenic diversity, and infection or vaccination generates long-term immunity. Viruses of this type are reliant on continued access to susceptible animal populations for their maintenance, with periodic and regular epidemic spread. Global eradication of rinderpest was achieved using appropriate management strategies coupled with vaccination of susceptible livestock. In contrast, viruses such as rotaviruses that are constantly endemic in livestock populations are reliant on genetic diversity and transient host immunity to ensure their perpetuation.

These viruses continually circulate and typically cause disease in only some individuals—those that are infected at critical stages of life, when they are most susceptible to infection because of lack of immune protection and other physiological and environmental factors.

Viruses evolve through a variety of mechanisms, but the key biological properties of individual virus strains are rarely determined by single nucleotide substitutions. Rather, important differences in the phenotypic properties of individual virus strains (eg, virulence, tropism, host range) are usually determined by multiple genes as polygenic traits.

Mutation

In productive virus infections of animals, a few virions gain entry and replicate through many cycles to generate millions or billions of progeny. During such replication cycles, errors in copying the viral nucleic acid inevitably occur, leading to an accumulation of mutations. Most mutations involve single nucleotide changes (syn. point mutations), but deletions or insertions of several contiguous nucleotides also occur. Mutations can be lethal, typically because the mutated virus has lost some vital information and can no longer replicate or compete with the wild-type virus. Whether a particular nonlethal mutation survives or not depends on whether the resultant phenotypic change in its gene product is disadvantageous, neutral, or affords the mutant virus some selective advantage.

Replication of cellular DNA in eukaryotic cells is subject to *proofreading*, an error-correction mechanism involving exonuclease activity. Because the replication of those DNA viruses that replicate in the nucleus is subject to the same proofreading, their mutation rates are probably similar to that of host-cell DNA (approximately 10^{-8} per incorporated nucleotide, ie, per nucleotide per replication cycle). RNA viruses show extremely high genetic variability and rapid evolution, ultimately due to their elevated rates of spontaneous mutation that range from 10^{-6} to 10^{-4} substitutions per nucleotide per round of copying. However, mutation rate estimates vary considerably, even for the same virus and depending on the cell type in which the virus replicates but this rate of nucleotide substitution is perhaps $100-10,000$-fold higher than the average rate in eukaryotic DNA. Of course, most of the nucleotide substitutions that occur during RNA virus replication are deleterious and the genomes containing them are lost. However, nonlethal mutations in the genome of RNA viruses accumulate very rapidly.

A Quasispecies Concept of Virus Evolution

Every virus species, as defined by conventional phenotypic properties, exists as a genetically dynamic, diverse population of virions in which individual genotypes have only a fleeting existence. Most individual viral genomes differ in one or more nucleotides from the *consensus* (or average) sequence of the population; over relatively short times, genotypic drift occurs as particular variants gain advantage. Genotypic drift over longer times leads to the evolution of substantially different viruses. Manfred Eigen, John Holland, and others introduced the term "quasispecies" to describe such diverse, rapidly evolving, and competing virus populations.

The evolution of quasispecies would be expected to be most conspicuous in viruses with large RNA genomes, in which nonlethal changes may accumulate rapidly. Indeed, the genomes of coronaviruses, the largest RNA genomes known, are fraught with "genetic defects." At the mutation rates noted earlier, perhaps one of 3000 nucleotides in every coronavirus genome would be changed in every round of replication; because coronavirus genomes contain about 30,000 nucleotides, every genome must differ from the next by at least one nucleotide. Further, coronavirus genomes undergo other more substantial mutations, including large deletions, which affect their pathogenicity. From this, one might wonder how coronaviruses or other RNA viruses can maintain their identities as pathogens over any evolutionarily significant period of time. Why have these viruses not mutated out of existence? The answer lies in the quasispecies concept, which is now well accepted for many viruses.

If viral nucleic acid replication was without error, all progeny would be the same and there would be no evolution of phenotypes. If the error rate was too high, mutants of all sorts would appear and the virus population would lose its integrity. However, at an intermediate error rate such as occurs with RNA viruses, the virus population becomes a coherent, self-sustaining entity that resembles a metaphorical "cloud" of variants centered around a consensus sequence, but capable of continuous expansion and contraction in different directions as new mutants continue to emerge within the population from a central master sequence and others disappear. Darwinian selection limits the survival of the most extreme mutants—extreme outliers do not survive—and favors variants near the center of the cloud, as these best achieve environmental "fit." At the center of the cloud is the *consensus genome sequence*, the average nucleotide at each genome locus as determined by conventional sequencing. However, the consensus sequence may not actually exist as one RNA molecule, whereas the so-called *master sequence* does as it is the genome that is most common in the population. The published genomic nucleotide sequence of most viruses reflects a random choice of starting material: one biological clone among many, more or less representative of the consensus sequence of the genome of the population as a whole, the cloud as a whole. shows evolution of a RNA virus cloud of variants ("mutant swarm") in its mammalian and insect hosts during the natural cycle of West Nile virus infection.
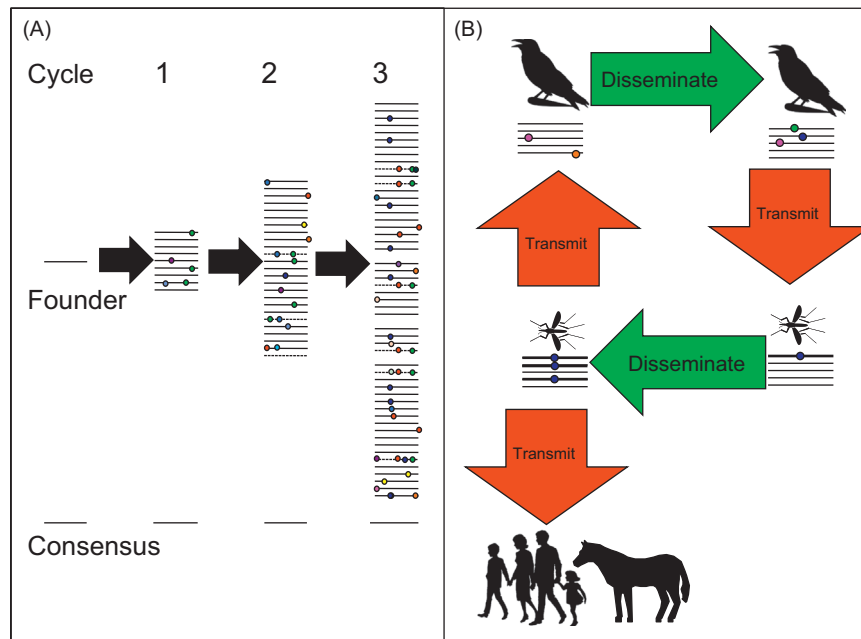
FIGURE 6.1 (A) Evolution of a RNA viral mutant swarm beginning with a founding genome (line). Mutant genomes (dots) arise; those with deleterious effects are negatively selected and do not survive to serve as templates for successive replication cycles, represented as arrows. Mutations that increase in frequency (blue dot in cycle 3) confer a phenotypic advantage (heavy line) and are positively selected. Despite constant evolution of the mutant swarm that leads to dynamic changes in the population, the consensus often remains unchanged, as in this example. The number of genomes in a population in a cell can reach several thousand, providing a highly complex swarm of mutants. The genomes that circumvent negative selection serve as founders that act as templates for subsequent replication cycles and play important roles in natural transmission, as in (B) mutant swarms in natural hosts during West Nile virus infection. Incidental human and equine hosts become infected and diseased but are incapable of transmitting back to mosquito vectors. Positively selected mutations (blue dot in mosquito vectors, for example) that confer changes in pathogenicity, tropism, and transmissibility can rise to dominate populations. Only dominant mutants have conventionally been identified and characterized. *Courtesy of L. Coffee, University of California.*

Genetic Recombination Between Viruses

When two different viruses simultaneously infect the same cell, genetic recombination may occur between the nucleic acid molecules during or after their synthesis. This may take the form of intramolecular recombination, reassortment, or reactivation (the latter, if one of the viruses has been inactivated).

Intramolecular Recombination

Intramolecular recombination involves the exchange of nucleotide sequences between different, but usually closely related, viruses during replication. It occurs with all double-stranded DNA viruses, presumably because of template switching by the polymerase. Intramolecular recombination also occurs among RNA viruses (eg, picornaviruses, coronaviruses, and togaviruses); for example, western equine encephalitis virus probably arose as a result of intramolecular recombination between an ancient Sindbis-like virus and eastern equine encephalitis virus. Such phenomena are likely to be more widespread among RNA viruses than was appreciated previously. Under experimental conditions, intramolecular recombination may even occur between viruses belonging to different families, as

exemplified by the now classical discovery of recombination between SV40 (a polyomavirus) and adenoviruses.

Recombination can occur between viral and cellular genetic material and, for at least some viruses, is also important in virus evolution. After all, viruses have access to the almost unlimited gene pool of their host cells, and they certainly have the capacity to incorporate and exploit genes that favor their growth and survival. The presence of cellular genes or "pseudogenes" within the genomes of retroviruses is well established, and the same has now been found for other viruses. For example, in influenza virus infections, proteolytic cleavage of the viral hemagglutinin by cellular proteases is essential for the production of infectious progeny. During the adaptation of nonvirulent influenza virus strains to chicken cells (which are nonpermissive for hemagglutinin cleavage), a pathogenic variant was isolated, containing an insertion of 54 nucleotides that was complementary to a region of host-cell 28S ribosomal RNA. This suggests template switching by the viral polymerase during viral RNA replication. This insertion seems to have changed the conformation of the viral gene product, the hemagglutinin, rendering it accessible to cellular proteases and, thereby, producing infectious virions in previously nonpermissive cells. Similarly, large DNA viruses

such as those of the *Asfarviridae* and *Poxviridae* include genes that encode immunomodulatory proteins similar to those normally produced by their animal hosts.

The pathogenetic consequences of cellular information being inserted into viruses by intramolecular recombination can be dramatic. The discovery that Marek's disease virus, an oncogenic herpesvirus of chickens, had been misclassified because it carries extra genes was particularly surprising. This virus had been previously considered to be a gammaherpesvirus, partly because all other oncogenic herpesviruses are members of this subfamily (*Gammaherpesvirinae*). Subsequently, as the genome of the virus was partially sequenced, it was realized that it is an alphaherpesvirus (subfamily *Alphaherpesvirinae*)—oncogenic strains of the virus had acquired oncogenic genes either from avian retroviruses or from the cellular homologues of retrovirus genes.

Equally surprising was the discovery of the molecular basis for the progression of bovine viral diarrhea to mucosal disease. When a cellular ubiquitin gene (or various other cell sequences) is inserted into the nonstructural gene *NS2-3* of noncytopathic bovine viral diarrhea virus strains, they become cytopathic in cell culture. Severe disease—that is, mucosal disease—occurs when such mutant viruses develop in the persistently infected animals that are produced following infection of the fetus with noncytopathic virus strains during the first 80−125 days of gestation. This complex pattern of infection and mutation explains the sporadic occurrence of universally fatal mucosal disease in calves and, in some cases, older animals.

Unlike other RNA viruses, retroviruses have no replicating pool of viral RNA. Although the genome of retroviruses is positive-sense single-stranded RNA, replication does not occur until the genomic RNA is transcribed into DNA by the virion-associated reverse transcriptase, and the resultant double-stranded DNA is integrated into the DNA of the host cell. However, both negative-strand and positive-strand recombinations occur between the two DNA copies of the diploid retrovirus genome, as well as between the DNA provirus and cellular DNA. In the latter instance, the retrovirus may pick up a cellular oncogene; such oncogenes are then incorporated into the viral genome to become viral oncogenes, which confer the property of rapid oncogenicity on the retrovirus concerned (see Chapter 14: *Retroviridae*).

Reassortment

Reassortment is a form of genetic recombination that occurs in RNA viruses with segmented genomes, regardless of whether they are single- or double-stranded and whether these involve few or many segments. Reassortment has been documented in families with 2 (*Arenaviridae* and *Birnaviridae*), 3 (*Bunyaviridae*), 6, 7, or 8 (*Orthomyxoviridae*), or 10, 11, or 12 (*Reoviridae*) genome

segments. In a cell infected with two related viruses within each of these families, an exchange of segments may occur, with the production of viable and stable reassortants. Such reassortment occurs in nature and is an important source of genetic variability; for example, bluetongue virus strains are often reassortants, sometimes containing genes similar or identical to those of live-attenuated vaccine viruses.

HOST AND ENVIRONMENTAL DETERMINANTS OF THE EMERGENCE OF VIRAL DISEASES

In order for a new viral disease to emerge, the causative virus must infect and successfully invade its host, bypassing the complex and sophisticated antiviral defenses that have evolved in all animals (see Chapter 4: Antiviral Immunity and Virus Vaccines). It is to be stressed that necessary host, virological, and environmental factors must, typically, coincide for a disease to emerge.

Crossing the Species Barrier—"Species-Jumping"

Genetic variation in viruses (as described earlier) can lead to the emergence of viruses with altered host range (ie, tropism), either to new animal species or humans. For example, it is proposed that porcine reproductive and respiratory syndrome virus arose from lactate dehydrogenase-elevating virus, presumably after a species-jumping event of the latter virus from mouse to pig. Similarly, phocid distemper, which affects seals, perhaps originated from a seal that contracted infection from a dog that was shedding canine distemper virus. Influenza A typifies a virus capable of interspecies transmission, often but not always as a consequence of rapid genetic change as a result of reassortment of gene segments. In addition to the regular and highly publicized transmission of novel influenza A viruses from birds to humans, similar exchanges can occur between other animal species—such as transmission of equine influenza virus to dogs.

Zoonotic agents are those that are transmitted from animals to humans, and the majority of new infectious diseases of humans discovered in the past half century or more are zoonoses. One example is the transmission to humans of a genetic variant of simian immunodeficiency virus that entered and spread amongst the human population as HIV; both HIV-1 and HIV-2 are believed to have arisen in humans within the past 100 years, HIV-1 from the chimpanzee and HIV-2 from the sooty mangabey. Although these viruses can experimentally infect nonhuman primates, they cause no disease. Other important examples include the henipah viruses (Hendra and Nipah), coronaviruses such as those responsible for Severe Acute Respiratory (SARS) and Middle East Respiratory (MERS)

syndromes, hantaviruses and arenaviruses, filoviruses such as the ebolaviruses, flaviviruses such as West Nile and Japanese B encephalitis viruses, the encephalitic equine alphaviruses, and bunyaviruses such as Rift Valley fever virus. In many instances, humans are dead-end hosts that play no part in the natural cycle of virus transmission, whereas in others, such as dengue, ebola, influenza A, and HIV, transmission between humans continues after the initial incursion of the virus into the human population.

It is increasingly apparent that bats harbor a number of zoonotic viruses with the potential to cause devastating diseases in humans. Bats are ubiquitous, and frequently coexist within or adjacent to human populations. Furthermore, bats typically reside in densely populated colonies that readily facilitate animal-to-animal transmission of viruses. Examples of viruses transmitted from bats to humans, amongst many, include rabies and related zoonotic bat lyssaviruses, Nipah and Hendra viruses, SARS coronavirus, and ebola and marburgviruses.

Rodents, like bats, occur in virtually every corner of the planet, which they coinhabit with humans. Rodents are important reservoirs of the hantaviruses that cause hemorrhagic fever with renal syndrome in the Far East and eastern Europe, and hantavirus pulmonary syndrome in the Americas. Similarly, rodents are the asymptomatic reservoir hosts of several arenaviruses that cause viral hemorrhagic fevers of people in portions of South America—for example, Lassa fever, Bolivian hemorrhagic fever, and Argentine hemorrhagic fever. Rodents also serve as reservoir hosts of some arboviruses (eg, louping ill virus, Venezuelan equine encephalitis virus) that can be transmitted to humans or other animals by the bites of infected vectors (ticks and mosquitoes).

Birds are also important reservoir hosts of a number of zoonotic viruses, most notably influenza A viruses. Furthermore, birds are the reservoir hosts of a variety of arboviruses, including alphaviruses such as eastern and western equine encephalitis viruses, and flaviviruses such as West Nile virus. Viruses are transmitted from infected birds to humans and animals by the bites of vector mosquitoes. Some of these viruses can cause disease in their bird reservoir hosts, whereas others invariably do not.

Environmental Factors

Ecological change inevitably alters the occurrence and distribution of viral diseases, especially those transmitted by arthropods. Human activities will continue to alter the distribution of viral diseases, both directly, through translocation of viruses and their vectors, and indirectly, through anthropogenic changes such as altered population demographics in response to climate change, the increasing blurring of the urban—rural interface, dynamic agricultural practices including livestock production systems, and destruction of long established ecosystems such as the tropical rain forests of South America.

Bioterrorism

The new world order has led to revised attitudes to biological warfare. In comparison with nuclear weapons and, to a lesser extent, chemical agents of mass destruction, biological agents combine relatively easy availability with maximum potential for destruction and terror. Economic and/or ecological catastrophes in animal populations are possible through the orchestrated and intentional use of several viruses discussed in this book.

SURVEILLANCE, PREVENTION, CONTROL, AND ERADICATION OF VIRAL DISEASES

PRINCIPLES OF DISEASE PREVENTION, CONTROL, AND ERADICATION

The prevention, control, and eradication of veterinary and zoonotic diseases are increasingly more complex in an era of global trade and intertwined political systems (eg, the European Union, North American Free Trade Agreement, Association of Southeast Asian Nations). Similarly, food production, processing, and distribution systems are also increasingly complex and intertwined, as exemplified by international trade in meat and poultry, dairy products, seafood, and shellfish, as well as pet birds, ornamental fish, and reptiles. With these changes has come increased public awareness of disease risks, and an increasing public expectation of the veterinary medical profession as the global steward of animal health and the related areas of environmental quality, food safety and security, animal welfare, and zoonotic disease control. All these responsibilities will require the application of the principles of preventive medicine, meaning that surveillance and time--honored investigative and disease prevention and control actions will increasingly be required.

Effective preventive medicine starts with the local practitioner, on the farm, ranch, feedlot, or poultry house, and in the veterinary clinic or animal shelter. In this respect, little has changed: the basic principles of good husbandry, knowledge of the prevalence of specific diseases and how they are transmitted, and the best methods for disinfection, vaccination, and vector control still apply. However, the requisite depth of knowledge of the scientific base underpinning preventive medicine practice is advancing rapidly—in many instances it will be the prevention and control of viral diseases that will lead the way for other veterinary medical risk assessment and risk management activities.

Nowhere in veterinary medicine is the adage, "an ounce of prevention is better than a pound of cure," more appropriate than in viral diseases. Apart from supportive therapy such as the administration of fluids for hydration of animals with viral diarrhea or the use of antibiotics to prevent secondary bacterial infections after viral respiratory diseases, there are no effective or practical treatments for most viral diseases of domestic animals, especially for livestock (see Chapter 4: Antiviral Immunity and Virus Vaccines). Nevertheless, there are well-proven approaches to the prevention, control, and even the eradication of important viral diseases of animals.

Viral disease prevention and control are based on diverse strategies, each chosen in keeping with the characteristics of the virus, its transmission pattern(s) and environmental stability, its pathogenesis and threat to animal health, productivity, and profitability, zoonotic risk, and so on. Exclusion is increasingly practiced for many pathogenic viruses of production animals, and comprehensive use of vaccines is also widely utilized—not solely for the protection of the individual animal, but also to build up a level of population immunity sufficient to break the chains of transmission. Hygiene and sanitation measures are especially important in the control of enteric (fecal−oral) infections in kennels and catteries, on farms and ranches, and in commercial aquaculture facilities. Arthropod vector control is the key to regional prevention of several arthropod-borne viral diseases. Test-and-removal programs continue to be used to eradicate important viral diseases of livestock and poultry. The risk of importation and spread of exotic diseases (syn. *foreign animal diseases*) into countries or regions is mitigated by regulatory controls at the border, quarantine and testing, and disease surveillance activities.

DISEASE SURVEILLANCE

The implementation of disease control programs and regulatory policy is critically dependent on accurate intelligence on disease incidence, prevalence, and spatiotemporal patterns of transmission. Surveillance of viral diseases provides this basic information through the systematic and regular collection, collation, and analysis of data on disease occurrence. Its main purpose is to detect trends—changes in the distribution of diseases, including incursions of viruses into countries and regions where historically they did not occur.

The need for data on the occurrence of infectious diseases has led to the concept of "notifiable" diseases, which veterinary practitioners are required to report to entral authorities such as state or national veterinary authorities. In turn, through regional or international agreements such as the World Organisation for Animal Health [Office International des Epizooties (OIE)], national authorities may elect or be obliged to inform other countries immediately of even the suspicion, let alone confirmation, of specific diseases in their country. Clearly, the contents of the list of notifiable diseases must be appropriate; if not, notification will be ignored. However, data provided by a system of notification can influence decisions on resource allocation for the control of diseases and the intensity of follow-up activities.

Many countries collect data on diseases that are not notifiable, providing useful data that can be used to develop strategies of prevention, especially by allowing calculation of benefit−cost ratios and indices of vaccine efficacy. Dependent on the characteristics of a particular disease, the availability of effective vaccines, and sensitivity and specificity of the diagnostic tests, progressive eradication programs can be planned and implemented, such as the relatively recent eradication of pseudorabies and classical swine fever from many countries.

Sources of Surveillance Data

The methods of surveillance used commonly for animal diseases are: (1) notifiable disease reporting; (2) laboratory-based surveillance; and (3) population-based surveillance. The key to surveillance is often the veterinary diagnostician and, especially, the veterinary practitioner. Although any one practitioner may see only a few cases of a particular disease, data from many practitioners can be accumulated and analyzed to reveal spatial and temporal trends in the occurrence of diseases. Another key to effective surveillance, especially for exotic or unusual animal diseases, is a heightened awareness among veterinary diagnosticians and practitioners— "when you hear hoofbeats, think horses, not zebras" may be good diagnostic advice to clinicians in general, but heightened awareness means that one should not totally dismiss the possibility that the hoofbeats may, indeed, be zebras.

Each country has its own system for collecting and collating data, and international agencies, such as the World Organization for Animal Health (OIE), coordinate information exchange between countries. There are several sources of information on disease incidence that are used by veterinary authorities in most countries, not all of which are pertinent for every disease:

1. Morbidity and mortality data assessed through information submitted to national, state, and local diagnostic laboratories and made available, with varying degrees of access, through national, regional, and international agencies, for example the OIE World Animal Health System at http://www.oie.int/wahis_2/public/index.php/home. Some of these data are also published through various annual reports, scientific journals, and so on.
2. Information from case and outbreak investigations, again, often linked to diagnostic laboratories and state and national veterinary investigations units.
3. Monitoring of virus activity by clinical, pathologic, serologic, and virologic examination of animals

presented for slaughter at abattoirs, tested for legal movement, examined in pathology laboratories, or used as sentinels to detect virus activity.

4. Monitoring of arthropod populations and viral infection rates, and monitoring of sentinel animals to detect arbovirus activity.
5. Specific serologic and virologic surveys.
6. Analyses of vaccine manufacture and use.
7. Reviews of local media reports of disease.
8. List servers, special interest group communications, and other Internet resources. It is anticipated that the mining of data available from social media will be used increasingly to detect unusual disease events.

Having collected data, it is important that they should be analyzed quickly enough to influence necessary follow-up measures. For example, data available from national databases are likely to be reliable and annotated, but often reflect information collected several weeks or even several months ago. In contrast, information gleaned from reviews of local media, from unusual social media activity, and from individual reports of unconfirmed disease on the internet may represent the earliest warning of an impending disease epidemic. However, such sources may provide well-intended, but false, information. Quick action when necessary and dissemination of information, particularly to local veterinary practitioners, is a vital component of effective surveillance systems. Caution must be exercised, however, to avoid unnecessary public alarm.

INVESTIGATION AND ACTION IN DISEASE OUTBREAKS

When there is a disease outbreak, it must first be recognized, usually at the level of primary veterinary care. This is not always easy when a new disease occurs or a disease occurs in a new setting. Investigation and actions may be described in the form of a "discovery-to-control continuum." The continuum involves three major phases, each with several elements.

Early Phase

Initial investigation at the first sign of an unusual disease episode must focus on practical characteristics such as mortality, severity of disease, transmissibility, and remote spread, all of which are important predictors of epidemic potential and risk to animal populations. Clinical observations and diagnostic findings (eg, gross pathology) often provide key early clues.

Discovery. The precise recognition of a new disease in its host population is the starting point. For diseases that are identified as endemic or present sporadically in a given animal population, outbreaks are usually handled by veterinary

practitioners working directly with diagnosticians, producers, and owners. For diseases that are identified as exotic or as having epidemic potential, further investigation and action depends on specialized expertise and resources.

Epidemiologic field investigation. Many of the early investigative activities surrounding a disease episode must be carried out in the field and diagnostic laboratory, not in the research laboratory. This is the world of "shoe-leather epidemiology."

Etiologic investigation. Identification of the etiologic virus is crucial—it is not enough to find a virus; its causative role in the episode must be established (see Chapter 5: Laboratory Diagnosis of Viral Infections).

Diagnostic development. It can be difficult after identifying a causative virus to develop and adapt appropriate diagnostic tests (to detect virus or virus-specific antibodies—see Chapter 5: Laboratory Diagnosis of Viral Infections) that can be used in the diagnostic laboratory and in epidemiologic investigations. This requires tests that are accurate (sensitive and specific), reproducible, reliable, and cost-effective, and also requires proof-testing of diagnostics in the field in the setting of the specific disease episode.

Intermediate Phase

The continuum progresses to the general area of risk management, the area represented not by the question: "What's going on here?" but by the question: "What are we going to do about it?" This phase may include expansion of many elements of the investigative process.

Focused research. The importance of focused research, aimed at determining more about the etiologic virus, the pathogenesis and pathophysiology of the infection, and related immunologic, ecologic (including vector biology, zoonotic host biology, etc.), and epidemiologic sciences, plays a major role in disease control programs.

Training, outreach, continuing education, and public education. Each of these elements requires professional expertise and adaptation to the special circumstances of the disease locale.

Communications. Risk communication must be of an appropriate scope and scale, utilizing the appropriate technologies, including news print media and social media.

Technology transfer. Diagnostics development, vaccine development, sanitation, and vector control, and many veterinary care activities require the transfer of information and specialized knowledge to those in need. This is especially true regarding information transfer from national centers to local disease control units.

Commercialization or governmental production. Where appropriate, the wherewithal for the production of diagnostics, vaccines, and so on must be moved from research-scale sites to production-scale sites. The capacity to involve private industry differs among countries and

with different viral diseases but in general, the private sector is more timely in commercializing production of vaccines.

Late Phase

Actions become increasingly complex as more expensive, specialized expertise and resources come into play.

Animal health systems development. This includes rapid case/herd reporting systems, ongoing surveillance systems, and records and disease registers. It also includes staffing and logistical support such as facilities, equipment, supplies, and transport. Often, the development of legislation and regulation is required. These elements are illustrated by the systems needed to control an outbreak of foot-and-mouth disease in an otherwise free country or region.

Special clinical systems. In some cases, isolation of cases by quarantine (usually requiring legal authorization and enforcement) and special clinical care and herd/flock management are necessary.

Public infrastructure systems. In some cases, new or additional sanitation and sewage systems, clean water supplies, environmental control, and reservoir host and vector control are required, which of necessity involves government or regulatory bodies. The largest epidemics may require substantial resources—for example, limiting the movement of animals on a national or regional scale, or test-and-slaughter programs—and similar actions often require special new funding and the involvement of international agencies.

Of course, not all these elements are appropriate in every episode of viral disease; rather, outbreaks of serious or exotic or zoonotic diseases typically evoke the greatest response.

STRATEGIES FOR CONTROL OF VIRAL DISEASES

Disease Control Through Hygiene and Sanitation

Intensive animal husbandry leads to accumulation in the local environment of feces, urine, hair, feathers, and so on, that may be contaminated with viruses; this is especially problematic with viruses that are resistant to environmental desiccation. To avoid this, intensive livestock units operate an "all in, all out" management system, by which the animal houses are emptied, cleaned, and disinfected between cohorts of animals. Hygiene and disinfection are most effective in the control of fecal−oral infections; they have much less effect on the incidence of respiratory infections. Efforts to achieve "air sanitation"

are generally unsuccessful, especially in intensive animal production systems with high population densities.

Nosocomial Infections

Nosocomial virus infections are less common in large animal veterinary practices, where animals are usually treated on the farm, than in companion-animal practices. Appropriate management can reduce the likelihood of nosocomial infections, and veterinary clinics usually require that all inpatients have current immunization. Clinics should be designed for easy disinfection, with wash-down walls and flooring and as few permanent fixtures as possible. They should also have efficient ventilation and air conditioning, not only to minimize odors, but also to reduce the aerosol transmission of viruses. Frequent hand washing and decontamination of contaminated equipment are essential. Similar strategies are required in animal shelters where large numbers of cats and/or dogs may be cohoused in an environment that is highly conducive to explosive outbreaks of a wide variety of viral diseases.

Disinfectants and Disinfection

Disinfectants are chemical germicides formulated for use on inanimate surfaces, in contrast to *antiseptics*, which are chemical germicides designed for use on the skin or mucous membranes. Disinfection of contaminated premises and equipment plays an important part in the control of diseases of livestock.

Viruses of different families vary greatly in their resistance to disinfectants, with enveloped viruses usually being much more sensitive than nonenveloped viruses. Most modern disinfectants inactivate viruses, but their effectiveness is greatly influenced by access and time of exposure: viruses trapped in heavy layers of mucus or fecal material are not inactivated easily. There are special problems when surfaces cannot be cleaned thoroughly or where cracks and crevices are relatively inaccessible, as in old timber buildings or the fence posts and railings of cattle and sheep yards. New data on the effectiveness of standard disinfectants or the release of new products requires access to updated information on the correct use of disinfectants. An excellent resource in this regard is the Center for Food Security & Public Health at Iowa State University (www.cfsph.iastate.edu).

Disease Control Through Eliminating Arthropod Vectors

Control of arbovirus infections relies, where possible, on the use of vaccines, because the large areas and extended periods over which vectors may be active make vector control difficult or, in many instances, impractical.

However, surveillance of vector populations (eg, mosquito larval counts) and/or the climatic conditions conducive to vector transmissions over wider geographical areas provides the justification for local vector control, both as a preventive and as a control strategy. For example, aerial spraying with ultra-low-volume insecticides has been used to prevent the establishment of mosquito populations carrying encephalitis viruses in some parts of North America, although there are issues pertaining to increasing mosquito resistance and environmental objections. Some countries have based their emergency arbovirus control program plans on aerial insecticide spraying. This strategy is aimed at rapid reduction of the adult female mosquito population in a defined area for a very short time.

Organophosphorus insecticides such as malathion or fenitrothion are delivered as an ultra-low-volume (short-acting) aerosol generated by spray machines mounted on backpacks, trucks, or low-flying aircraft. Spraying of the luggage bays and passenger cabins of aircraft with insecticides reduces the chances of intercontinental transfer of exotic arthropods, whether infected or noninfected.

Exclusion of ticks has proven successful in the control of African swine fever in endemic regions; however, control is more difficult in free-ranging animals.

Disease Control Through Quarantine

Movement of domestic animals across international and even state borders can be regulated in countries where there are appropriate veterinary services and regulatory infrastructure. Quarantine remains a cornerstone in many animal disease control programs. A period of quarantine, with or without specific etiologic (eg, PCR) or serologic testing (see Chapter 5: Laboratory Diagnosis of Viral Infections), is usually a requirement for the importation of animals from another country, and similar requirements may be enforced within a country or region for the control or eradication of specific infectious agents.

As international movement of live animals for breeding purposes and exhibition has increased, so has the risk of introducing disease. Before the advent of air transport, the duration of shipment usually exceeded the incubation period of most diseases, but this is no longer the case. With the ever-increasing value of livestock, national veterinary authorities have tended to adopt stricter quarantine regulations to protect their livestock industries. Complete embargoes on importation are imposed for some animals by some countries. The concept of quarantine (Italian, *quarantina*: originally 40 days during which, in medieval times, ships arriving in port were forbidden to land freight or passengers if there was a suspicion of a contagious disease), where animals were simply isolated and observed for clinical signs of disease for a given period of time, is now augmented and often expedited by extensive laboratory testing designed to detect previous exposure to selected viruses or a carrier state. Laboratory testing requirements are set down in detailed protocols and are supported by national legislation.

Historically, the quarantine of animals has been a successful method for preventing the introduction of many diseases; however, other diseases may be introduced in animal products (eg, foot-and-mouth disease in meat products) or by virus-infected arthropods (eg, bluetongue). It must also be recognized that most countries have land boundaries with their neighbors and cannot control human and wildlife movement easily; thus, countries are expected to confirm their disease status to the World Organisation for Animal Health, which is the responsible international body. In addition to its central role in the reporting of livestock diseases globally, this organization also is responsible for harmonizing diagnostic testing and the creation of internationally agreed criteria for the safe movement of animals and animal products. However, problems persist that are often social, economic, and political rather than scientific—for example, smuggling of exotic birds may play a significant role in the introduction of Newcastle disease and fowl plague (highly pathogenic avian influenza) viruses into susceptible avian populations.

Disease Control Through Vaccination

Each of the foregoing methods of control of viral diseases is focused on reducing the risk of infection, whereas vaccination is intended to render animals resistant to infection with specific viruses. Immune animals cannot participate in the transmission and perpetuation of such viruses in the population at risk. Thus, vaccination can reduce the circulation of virus in the population at risk, as confirmed in countries where there is widespread vaccination of dogs against canine distemper and infectious canine hepatitis. Relaxation of vaccine usage, however, can have devastating consequences as, for example, in Finland in the 1990s, when canine distemper virus reemerged into a dog population in which vaccine usage had declined.

Safe and effective vaccines are available for many common viral diseases of animals. They are especially effective in diseases with a necessary viremic phase, such as canine distemper and feline panleukopenia. It has proved much more difficult to immunize effectively against infections that localize only in the alimentary or respiratory tracts.

Vaccination has been utilized extensively, and with varying success, in programs for the control and/or eradication of certain diseases. For instance, vaccination was key to the recent global eradication of rinderpest. Vaccination has been widely used in efforts to control foot-and-mouth disease in portions of South America and Asia, in conjunction with

other disease control activities. The use of genetically engineered vaccines with accompanying serological tests that distinguish vaccinated from naturally infected animals (DIVA) are especially useful in control programs (see Chapter 4: Antiviral Immunity and Virus Vaccines).

Influence of Changing Patterns of Animal Production on Disease Control

Relatively recent changes in systems of food animal management and production have had profound effects on disease patterns and control. Systems of animal production for food and fiber are extensive in much of the world, typified by the grazing of sheep and cattle across grasslands, as in the Americas and Australia, or by the movement of small herds of cattle or goats across the Sahel by nomadic tribes in Africa. Chickens and swine were penned and housed centuries ago, but intensive animal production systems, particularly for chickens and swine and, to a lesser extent, for cattle and sheep, were established only relatively recently. Concern over the welfare of animals in these intensive units has led to the reintroduction of more traditional husbandry in many countries.

Infectious diseases, particularly viral diseases, have often been the rate- and profit-limiting step in the development of intensive systems. Significant aspects of intensive animal production include the following:

1. The bringing together of large numbers of animals, often from diverse backgrounds, and confining them to limited spaces, at high density.
2. Asynchronous removal of animals for sale and the introduction of new animals.
3. The care of large numbers of animals by few, sometimes inadequately trained, personnel.
4. Elaborate housing systems with complex mechanical systems for ventilation, feeding, waste disposal, and cleaning.
5. Limitation of the husbandry system to one species.
6. Manipulation of natural biologic rhythms by use of artificial daylight, estrus synchronization, etc.
7. Use of very large batches of premixed, easily digestible foodstuffs.
8. Improved hygienic conditions.
9. Isolation of animal populations.

Intensive animal production units, such as cattle feedlots, swine units, dry-lot dairies, and broiler chicken houses, colocalize extraordinarily large numbers of animals in very close proximity. Three consequences follow upon these situations:

1. The conditions favor the emergence and spread of endemic infectious diseases, as well as opportunistic infections.
2. The introduction of nonendemic viruses poses a greater risk to such populations; although many farms are designed to provide reliable barriers against such introductions, many others are not.
3. These conditions favor several infections working synergistically, further complicating diagnosis, prevention, and therapy.

Disease is a component of the current concerns over welfare in intensive systems, but viral diseases are unlikely to change these intensive livestock production systems because of their economic efficiency. Nevertheless, there is great merit in improving these production systems by minimizing disease losses, thereby increasing yields and lowering costs. The chief constraint is management, with the solution requiring the introduction of modern epidemiologic methods into the training and experience of veterinarians and other animal scientists involved in livestock production.

The increased adoption of organic farming methods and the traditional extensive farming of livestock that is practiced in many countries increases the possibility of interaction of livestock with other species, and wildlife in particular, eg, free-range poultry with wild water fowl. Frequent and extensive movement of domestic livestock, wildlife species, and people exacerbates the spread of infectious diseases, especially in regions where wildlife harbor viruses that are contagious to livestock or humans. These are matters of national and international concern, not only for humanitarian reasons, but because of the risk of the international transfer of exotic viruses of livestock.

The situation with companion animals is quite different, but the risk of infectious diseases varies greatly between the single, mature-age household dog, cat, or pony and the large, sometimes disreputable, breeding establishments for these species ("puppy farms," for example) in which several hundred animals, of all ages, are kept and bred. Similarly, although animal shelters provide a necessary refuge for unwanted cats and dogs, the intensive cohousing of large numbers of stressed animals provides a fertile environment for transmission of viral diseases. The movement of horses for athletic events, breeding, and commerce greatly increases the risk of translocation of viral diseases to free regions or countries, as illustrated by recent outbreaks of equine influenza in both Australia and South Africa.

ERADICATION OF VIRAL DISEASES

Disease control, whether by vaccination alone or by vaccination in combination with the various methods described earlier, is a continuing process that must be maintained as long as the disease is of economic and/or social importance. Successful eradication of a disease that is endemic often requires a sustained and substantial

financial commitment. If a disease can be eradicated within a country so that the virus is no longer present anywhere except in secure laboratories, control measures within that country are no longer required and costs are decreased permanently. Surveillance to prevent the reintroduction of the disease into the country is still necessary. Close cooperation between veterinary services and agricultural industries is essential, which requires that disease eradication programs be justified politically and by benefit−cost and risk analyses. As programs proceed, they must ensure feedback of information on progress (or problems) directly to those involved and to the public via the media.

Foot-and-mouth disease has now been eradicated from a number of countries in which it was once important, but outbreaks of the disease in previously free countries continue to occur regularly, often with devastating economic consequences. An outbreak in Taiwan in 1997 illustrates vividly the impact of this disease on the agricultural exports of a small country, and is a salient reminder of the importance of this disease. Capitalizing on its geographical advantage of being an island, Taiwan had been free of foot-and-mouth disease since 1929, while most neighboring countries of continental Asia remained endemically infected. Before the outbreak, Taiwan had a robust export market of pork to Japan (6 million pigs per year), which represented 70% of its pork exports and approximately 60% of its pig production. The presence of foot-and-mouth disease on the island went unnoticed initially, and when the extent of the epidemic became apparent all exports of pork ceased and international markets were lost. Factors that contributed to the very rapid spread of the virus included high densities of pigs and ineffective control of animal and product movement until the epidemic was well into its course. There was no legislation against the feeding of waste food, and several outbreaks probably originated from infected pig products. The procedures used for the disposal of pigs were chaotic, and probably resulted in further dissemination of virus. During the first 100 days of the epidemic, some 60 outbreaks were reported each day—quite a challenge for any veterinary service!

A similar but even more economically devastating outbreak of foot-and-mouth disease occurred in the United Kingdom in 2001, some 34 years after the last such outbreak. The 2001 outbreak precipitated a crisis that led to the slaughter of more than 10 million cattle and sheep, and which had a devastating impact on British agriculture, tourism, and the economy: this event is estimated to have cost the British economy up to US$16 billion. Similarly, devastating foot-and-mouth disease epidemics occurred in Japan and North and South Korea in 2010−2011, and again in Korea in 2014−2015.

So far, *global* eradication has been achieved for only one human disease: smallpox. The last endemic case of smallpox occurred in Somalia in October 1977. Global eradication was achieved by an intensified effort led by the World Health Organization, which involved a high level of international cooperation and made use of a potent, inexpensive, and very stable vaccine. However, mass vaccination alone could not have achieved eradication of the disease from the densely populated tropical countries, where it remained endemic in the 1970s, because it was impossible to achieve the necessary high level of vaccine coverage in many remote areas. A revised strategy was implemented in the last years of the eradication campaign, involving surveillance and containment: cases and niches where transmission was current were actively sought out and "ring vaccination" (vaccination of everyone in the area, first in the household and then at increasing distances from the index case) was implemented. The global smallpox eradication campaign was a highly cost-effective operation, especially in light of the ongoing cost for vaccination, airport inspections, and other interventions made necessary by the existence of smallpox, to say nothing of costs and complications of vaccination, the misery, and deaths from smallpox. A similar global effort to eradicate polio has not met with similar success to date as the disease is still endemic in Afghanistan, Nigeria, and Pakistan.

Rinderpest is the first animal disease to have been globally eradicated. Rinderpest was a devastating disease of cattle in Europe before it was finally eliminated from the continent in 1949, and was a scourge in sub-Saharan Africa ever since livestock farming was introduced in the late 1800s. Remarkably, it was very nearly eliminated from Africa in the 1980s by massive cattle vaccination programs, but regional wars and violence interceded, programs were stopped, and the disease made a rapid comeback in many areas before its eventual eradication. The lessons learned from these vaccination programs, additional lessons from the success in eradicating smallpox and in the control of polio, and the availability of an effective vaccine, contributed to successful global eradication of rinderpest in 2011. Successful regional/country eradication of Newcastle disease, fowl plague, classical swine fever, foot-and-mouth disease, infectious bovine rhinotracheitis, pseudorabies, equine influenza, bovine leukemia, and even bovine viral diarrhea raises the question of whether there are other animal diseases that might one day be eradicated globally. The viruses that cause diseases most amenable to eradication typically have no uncontrollable reservoirs, they exist as one or few stable serotypes, and safe and efficacious vaccines are available to prevent infection. Of course, once a virus is eradicated from a given animal population, that population becomes wholly susceptible to any new introduction of that specific virus.