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Epidemiology is the study of the distribution, the dynamics, and the determinants of diseases in populations. The risk of virus infection and/or disease in a human population is determined by the characteristics both of the virus, and of susceptible individuals and of the host population such as innate and acquired resistance. In addition, virus transmission is affected by behavioral, environmental, and ecological factors. Virus epidemiology aims to meld these factors using quantitative measurements to provide a rational basis for explaining the occurrence of virus diseases and for directing disease-control measures, in particular the identification of outbreak sources and how best to implement prevention strategies. Epidemiology can also help to clarify the role of viruses in the etiology of diseases, understanding the interaction of viruses with environmental determinants of disease, determining factors affecting host susceptibility, clarifying modes of transmission, and the testing of vaccines and therapeutics on a large scale.

**Epidemics** are peaks in disease incidence that exceed the endemic baseline or expected rate of disease. The size of the peak required to constitute an epidemic is arbitrary and is related to the background endemic rate and the rate of clinical to sub-clinical infection. Sometimes a few cases of a disease that arouse anxiety because of their severity, for example encephalitis, will be loosely termed an “epidemic” whereas a few cases of influenza will not, but the term strictly implies unusually wide and rapid spread of infection within the population.

**MECHANISMS OF VIRUS SURVIVAL**

Because viruses, unlike most bacteria, cannot replicate outside of living cells, 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 often produce more infectious virus than inapparent infections, the latter are generally more numerous and, because these do not restrict the movement of infectious individuals, they can provide a major mechanism of viral dissemination. Epidemiologists recognize three different patterns of virus survival in mammalian hosts, distinguished through use of virus reservoirs: acute self-limiting infections with no reservoir, persistent infections with a reservoir in humans, and involvement of an animal reservoir.

Most viruses have a principal mechanism for survival, but if this mechanism is interrupted, for example, by a sudden decline in population of the host species due to another disease or a short-term climate change, alternate mechanisms, previously less apparent, may emerge. This should be remembered when relating the epidemiology of a specific disease to a particular mechanism of survival, as proposed in Table 13.1.

An appreciation of the pathogenesis and clinical features of a particular infection is valuable in designing and implementing control programs. For example, the knowledge that variola virus caused an acute self-limiting infection in which the vast majority of infected individuals showed clinical disease, and that it had no animal host, was important in the successful eradication of smallpox.

The majority of human viral infections fall into the category of acute self-limiting infections. Optimum transmissibility is crucial, and with viruses that cause systemic infections with lifelong immunity, perpetuation is possible only in large, relatively dense populations. Viruses that cause superficial mucosal infections with short-lived immunity may survive in somewhat smaller populations, and a capacity to survive in a circumscribed population may be enhanced by antigenic drift (see below).

**VIRAL SHEDDING AND ROUTES OF TRANSMISSION**

Transmission cycles require virus entry into the body, replication, and shedding with subsequent spread to another host. Molecular and cellular aspects of entry and shedding were described in Chapter 4: Virus Replication; here only those aspects that are relevant to epidemiology are discussed.
TABLE 13.1 Different Survival Mechanisms Used by Viruses in Nature

| Features of Infection | Survival Mechanism | Virus |
|-----------------------|-------------------|-------|
| Acute self-limiting infection—lifelong immunity | No reservoir; need large population with continuing chain of transmission | Measles, mumps, rubella, polio<sup>a</sup>, hepatitis A<sup>a</sup>, enteroviruses<sup>a,c</sup>, dengue |
| Acute self-limiting infection—immunity more short-lived | No reservoir; reinfections occur, virus can survive in smaller-sized population | Respiratory syncytial virus, rotavirus<sup>b</sup>, influenza<sup>b</sup>, coronaviruses, rhinoviruses<sup>c</sup> |
| Persistent infection-intermittent replication +/− shedding | Human reservoir; infected individuals can provide lifelong source of virus | Herpes simplex, varicella-zoster, CMV, EBV, other herpesviruses |
| Persistent infection—continuous replication | Human reservoir; infected individuals can provide lifelong source of virus | HIV, HBV, HCV, HTLV-1, human papillomavirus |
| Zoonoses—no human–human spread | Survival depends on enzootic infection in animal reservoir and transmission to humans | Most arboviruses except dengue, yellow fever (urban cycle), Avian influenza, rabies, Hendra |
| Zoonoses—human–human spread also significant | Survival depends on enzootic infection in animal reservoir and transmission to and between humans | Marburg/Ebola, Hantaan, Nipah, dengue, yellow fever (urban cycle) |

<sup>a</sup>Viruses are resistant and can survive in the environment for days.

<sup>b</sup>Antigenic shift and drift helps new infections overcome preexisting immunity.

<sup>c</sup>Existence of many serotypes allows new infections with related serotypes.

Virus transmission (Fig. 13.1) may be horizontal or vertical; however, most transmission is horizontal, that is, between individuals within the population at risk. More so than in the case with bacteria, different viruses tend to use specific defined transmission routes that are ultimately determined by factors such as the physical properties of the virion, route of shedding, and aspects of pathogenesis such as cell tropism. These routes are primarily defined by the different ways used by different viruses to broach the continuous external epithelial lining of the body. How the particular route of entry can be an important determinant in pathogenesis is discussed in Chapter 7: Pathogenesis of Virus Infections; equally, the route of entry is a major factor in determining the patterns of occurrence, mode of spread, and risk populations for each virus infection.

Shedding of virus usually occurs from one of the body openings or surfaces also involved in the entry of viruses. With localized infections the same body openings are involved in both entry and exit (see Fig. 7.1); in generalized infections a greater variety of modes of shedding is recognized, and some viruses are shed from multiple sites, for example, hepatitis B virus, HIV, and cytomegalovirus in semen, cervical secretions, milk, and saliva. The amount of virus shed in an excretion or secretion is important in relation to transmission. Very low concentrations may be irrelevant unless very large volumes of infected material are transferred; on the other hand some viruses occur in such high concentrations that a minute quantity of material, for example, less than 1 μl, can transmit infection.

**Respiratory and Oropharyngeal Route**

Many different viruses causing localized disease of the respiratory tract are shed as aerosols in the mucus or saliva expelled from the respiratory tract during coughing, sneezing, and talking. Viruses are also shed from the respiratory tract in several systemic infections, such as in measles, chickenpox, and rubella. A few viruses, for example, the herpesviruses, cytomegalovirus, and Epstein-Barr virus, are shed into several systemic infections, such as in measles, chickenpox, and rubella. A few viruses, for example, the herpesviruses, cytomegalovirus, and Epstein-Barr virus, are shed into several systemic infections, such as in measles, chickenpox, and rubella. A few viruses, for example, the herpesviruses, cytomegalovirus, and Epstein-Barr virus, are shed into...

Aerosols are most infectious early in a respiratory infection at the peak of virus replication, but there is also variation from individual to individual, and some patients, for reasons not well understood, seem to be more infectious than others (“super shedders”). There are three distinct components of spread of respiratory viruses. Small-droplet aerosols (<10 μm diameter particles) can create rapid explosive outbreaks and spread to more distant contacts (>1.8 m). These particles are more likely to settle lower down the respiratory tract. Second, large-droplet aerosols (10 to 100 μm diameter) sink to the ground more quickly, and therefore transmission needs closer contact between source and recipient (<0.9 m); spread may be slow, intermittent, and without clustering. These particles are mostly trapped in the upper airways. Third, spread occurs when fomites, including tissues, ward equipment, and household objects become contaminated with respiratory secretions or aerosol droplets and contacts transfer this material to their own...
respiratory tracts; this mode of spread particularly involves those in close contact with others under conditions of poor hygiene (Box 13.1).

Environmental sources of airborne transmission include virus-contaminated dust, thought to be the source of arenavirus infections, and aerosols of infected urine from rodents (arenaviruses) or bats (rabies). However, most respiratory viruses, being enveloped, are relatively labile and do not survive long outside the body unless kept moist in secretions.

FIGURE 13.1 Modes of transmission of human viral diseases. Modified from Mims, C.A., 1982. “The Pathogenesis of Infectious Disease,” second ed., Academic Press, London.
BOX 13.1 Transmission Routes via the Respiratory Tract

Respiratory transmission is a very efficient way to quickly infect a large number of contacts and spread virus globally (compare influenza with HIV). There are two mechanisms:

1. **Inhalation of aerosol.** Humans filter ~600 liters of air per hour when breathing at rest. Aerosols are created especially by sneezing and coughing, less by talking.

   - Large droplets (>10 μm) soon sink to the floor, while small droplets can spread further but dry out and virus becomes inactivated; this is why the atmosphere does not remain infective for long.

   - Seasonality of respiratory infections is affected by increased virus survival in cooler temperatures, seasonal differences in social activities, school attendance patterns, and many other factors.

2. **Contaminated objects.** Infected respiratory secretions contaminate tissues, environmental surfaces and objects, hands. Shaking hands, handling objects etc. provides a pathway for virus to the nose and mouth of a new person.

### Gastrointestinal Route

Enteric viruses are shed in the feces and vomit, and the more voluminous the fluid output the greater is the environmental contamination caused. These viruses tend to be harder and able to survive environmental conditions longer outside the body than the enveloped respiratory viruses. Two epidemiological patterns are seen: (1) a point source outbreak occurs when many people ingest contaminated food or water, for example at weddings or other functions. This particularly occurs with salads, uncooked shellfish, or through drinking unsafe river water or well water contaminated with sewage, and (2) person-to-person spread by the fecal–oral route is more gradual and occurs more efficiently in households without running water, hand-washing facilities, or toilets, and where there is poverty and a lack of education.

### Cutaneous Route

The unbroken skin normally presents an impermeable barrier to virus entry. Virus shedding from the skin is usually so insignificant that individuals with systemic blood-borne infections, for example, should be reassured that their unbroken skin does not present a continuing risk to their social contacts. However, minor skin abrasions can be an important source of virus for diseases in which transmission is by direct contact, for example, molluscum contagiosum and warts. Blood-borne infections (see below) can be shed through bleeding from broken skin, and hepatitis B has been shown to spread by inapparent horizontal transmission between children, particularly in poor socio-economic conditions with overcrowding and/or prevailing skin disease. However, blood-borne infections are of course typically spread by one of a number of ways of directly introducing infected blood parenterally into a recipient (e.g., by injection, needle-sharing, or transfusion).

Several poxviruses may be spread from animals to humans, and sometimes from humans to animals through contact with skin lesions, for example, the viruses of cowpox, vaccinia, orf, and pseudocowpox. Although skin lesions are produced in several generalized diseases, virus is not shed from the maculopapular skin lesions of measles, or from the rashes associated with picornavirus, togavirus, or flavivirus infections. Herpesvirus infections, on the other hand, produce vesicular lesions in which virus is plentiful in the fluid of the lesions. Even here, however, virus shed in saliva and aerosols is much more important as far as transmission is concerned, than that shed via the skin lesions.

Finally, mention should be made of the transmission of rabies virus and B virus (Macacine herpesvirus 1 or herpesvirus simiae) through the skin by the bite of an infected animal.

### Genitourinary Route

Many viruses can be found in semen or vaginal secretions. Sexual transmission of virus infections by mucosal contact can be efficient because the virus is kept moist and does not need to survive long outside the body; however dissemination through risk populations by this route is usually slower than by respiratory spread because involvement of multiple contacts is usually slower. Studies particularly with HIV have shown that sexual transmission is enhanced when there is a greater number of consecutive partners, when concurrent genital mucosal tears or intercurrent infections (e.g., ulcerating STDs) are present, and when the male involved is not circumcised. The most important examples are HIV, HBV, human papillomavirus, and herpes simplex type 2, although other herpesviruses, hepatitis B, and HTLV I are also sexually transmitted with ease.

**Viruria** is life-long in arenavirus infections of rodents and constitutes the principal mode of contamination of the environment by these viruses. However, while a number of human viruses, for example, mumps virus and cytomegaloviruses, replicate in tubular epithelial cells in the kidney and are shed in the urine, this is not a major source of transmission from human to human.

### Blood-Borne Route

Just as viremia is an important route of virus dissemination within individual hosts, so it is between hosts. Hepatitis B, C, and D viruses, HIV, and HTLV were once commonly spread by blood transfusion, but the risk has been obviated...
by comprehensive testing of donated blood. Highly sensitive tests, for example polymerase chain reaction (PCR), are often used because of the extra risk caused by the large volume of blood transfused and the usual compromised health of recipients. Today in most countries, blood-borne transmission of these viruses is more a problem among intravenous drug users due to contaminated needles and injecting paraphernalia. Of course, blood is the usual source from which arthropods (e.g., mosquitoes, ticks, sandflies) acquire viruses during the course of taking a blood meal. Less commonly, some arthropods (e.g., horseflies, other biting flies) transmit viruses passively by contamination of their mouth parts and interrupted blood feeding on multiple hosts.

Despite this, in most instances blood-borne viruses are not shed from the unbroken skin of an infected person, and transmission by normal skin contact is negligible.

**Ophthalmic Route**

Virus infection can be introduced into the eye from the patient’s fingers (herpes simplex, vaccinia), from swimming pools (adenoviruses), from inadequately sterilized ophthalmic equipment (adenoviruses, prions), via aerosols (enterovirus 71), or via the blood stream in a systemic infection (measles).

**Milk-Borne Route**

Several viruses, for example, cytomegalovirus, HIV-1, and HTLV-1, are excreted in milk, which may serve as a route of transmission to the newborn infant. In some situations, the additional risk of transmission from an infected mother by breastfeeding may be much smaller than the risk of vertical transmission already incurred during the birth process; breastfeeding may still be recommended where infectious disease or malnutrition is a common cause of death in infancy, despite the additional risk of transmission incurred.

**Vertical Transmission**

Transmission of virus from the mother to the embryo, fetus, or newborn, is an important instance of cross-generational transmission that facilitates survival of some viruses in nature. The three situations where this occurs are described in Chapter 7: Pathogenesis of Virus Infections, namely (1) via the integration of proviral DNA directly into the DNA of the germline of gametes and fertilized eggs, (2) transplacental spread during pregnancy, and (3) perinatal or postnatal spread via saliva, milk, or other secretions. Vertical transmission of a virus may be lethal to the fetus and cause abortion, it may be associated with congenital disease or congenital abnormalities, or it may cause a sub-clinical infection.

In the case of HIV and hepatitis B, vertical transmission introduces infection to a new generation of infants who are then capable of transmitting infection to succeeding birth cohorts for many years to come. In addition, vertical transmission in arthropod vectors is an important mode of perpetuation of some arthropod-borne viruses.

**No Shedding**

Many sites of viral replication are a “dead end” in regard to transmission to other hosts, for example, no virus is shed from the brain or other organs that do not communicate with a body opening or the body surface. One might question how this could benefit the long-term survival of the virus in nature, but the stepwise augmentation of virus titer by replication in cells located in internal organs is often an important pre-requisite for shedding from another site, or for infection of blood-sucking arthropods. In animals such as mice and chickens, many retroviruses are not shed, but are transmitted directly to the next generation via the germline, or by transplacental spread, as described above.

**FACTORS AFFECTING THE DYNAMICS OF VIRAL INFECTIONS**

**Transmissibility**

Transmissibility is affected by physical properties of the virus, the extent and nature of shedding from the body, and social interactions between hosts. Obviously, the shedding of high titers of infectious virus enhances human-to-human transmission. Respiratory viruses tend to be shed over a relatively brief period of a few days but are expelled at high concentration as an aerosol generated by explosive sneezing or coughing, thus ensuring transmission to close contacts. The complex usage of different receptors by different influenza variants can determine virus transmissibility between humans (see Chapter 25: Orthomyxoviruses). Enteric viruses are also shed in large numbers but usually for a longer period (a week or more) in feces. These viruses may contaminate hands, fomites, food, and water. Enveloped respiratory viruses are relatively labile, especially during summer or in the tropics year-round. In contrast, many enteric viruses are non-enveloped and may survive for several days or weeks in water or dust, or on fomites, as is also true for poxviruses, adenoviruses, papillomaviruses, and hepatitis A and B viruses.

Improvements in socio-economic conditions, sanitation, and education have slowed the transmission of a number of common childhood infections, resulting in many infections being acquired at an older age. Some infections cause more clinical disease in older age groups, and thus these
improvements may result in a paradoxical increase in cases of clinical disease (Box 13.2).

Fig. 13.2 defines the different time intervals relevant to a typical acute transient infection, and Table 13.2 sets out these parameters for some common human viral diseases. In many infections, such as in measles and chickenpox, persons become contagious a day or so before they themselves become ill.

The zoonoses, whether involving domestic or wild animal reservoirs, usually occur only under conditions where humans are engaged in activities involving close contact with animals (Table 13.3) or if the viruses are transmitted by arthropods (Table 13.4).

Seasonality

Many viral infections show a pronounced seasonal variation in incidence. In temperate climates, arbovirus infections transmitted by mosquitoes or sand-flies occur mainly during the summer months when the vectors are most numerous and active. Infections transmitted by ticks occur most commonly during the spring and early summer months. More interesting, but also more difficult to explain, are the variations in seasonal incidence of infections in which humans are the only host.

Table 13.5 shows the season of maximal incidence of several human respiratory, enteric, and generalized infections. In temperate climates most respiratory infections are mainly prevalent in winter or to a lesser extent in spring or autumn. Annual winter outbreaks of severe respiratory syncytial virus infections in infants are a feature in temperate climates (Fig. 13.3); epidemics of influenza also occur almost exclusively in the winter, but these may vary greatly in extent from year to year. Many of the rash diseases of childhood transmitted by the respiratory route reach a peak in the spring. Among the enteric virus infections, seasonality varies with the etiologic agents: the incidence of a number of enterovirus infections (in common with most enteric bacterial infections) is greatest in the summer, but caliciviruses show no regular seasonal patterns and rotaviruses tend to be more prevalent in the winter months. Infections with the herpesviruses (HSV, cytomegalovirus, and EB virus), all transmitted by intimate contact with saliva and other bodily secretions/excretions, show no seasonal variations in incidence; neither do other sexually transmitted diseases. The patterns shown in Table 13.5 are found in both the northern and southern hemispheres. Different factors probably affect seasonality in the tropics, where wet and dry seasons tend to replace summer and winter. The peak incidence of measles and chickenpox is late in the dry season, with an abrupt fall when the rainy season begins, whereas influenza and rhinovirus infections reach a peak during the rainy season.
Both biological and sociological factors may play a role in these seasonal variations. Measles, influenza, and vaccinia viruses survive in air better at low rather than high humidity, whereas polioviruses, rhinoviruses, and adenoviruses survive longer at high humidity. All viruses survive longer in aerosols, and at lower temperatures. These situations correspond with the conditions prevalent during those seasons when infections due to these viruses are most prevalent. It has also been suggested that there may be seasonal changes in the susceptibility of the host, perhaps associated with changes in nasal and oropharyngeal mucous membranes, such as drying as a result of smoke, central heating, or air conditioning.

Second, seasonal differences in social activities also markedly influence the opportunities for transmission of viruses, especially by the respiratory route. Although experiences in the Arctic and Antarctic show that cold weather alone is not enough to influence the incidence of common colds and other respiratory infections, the crowding into restricted areas and ill-ventilated vehicles and buildings that occurs in temperate climates during the winter months promotes the transmission of respiratory viruses. In places subject to monsoonal rains, the onset of the rains early in summer is accompanied by a greatly reduced movement of people, both in daily life and to fairs and festivals. While this may reduce the opportunity for exchange of viruses with those from other villages, confinement to smoke-filled dwellings maximizes the opportunity for transfer of respiratory viruses within family groups.

In urban communities young children appear to be particularly important as the persons who introduce viruses into families from school and from neighbors’ children, because they have not yet acquired the immunological memories of past infections, and often shed larger amounts of virus compared to adults.

### TABLE 13.2 Epidemiological Features of Important Human Viral Diseases

| Disease                     | Mode of Transmission | Incubation Period\(^a\) (days) | Period of Infectivity\(^b\) | Clinical:Sub-clinical Ratio\(^c\) |
|-----------------------------|----------------------|-------------------------------|-----------------------------|----------------------------------|
| Influenza                   | Respiratory          | 1–2                           | Short                       | Moderate                         |
| Common cold                 | Respiratory          | 1–3                           | Short                       | Moderate                         |
| Bronchiolitis               | Respiratory          | 3–5                           | Short                       | Moderate                         |
| Dengue                      | Mosquito bite        | 5–8                           | Short                       | Moderate                         |
| Alphavirus encephalitis     | Mosquito bite        | 4–10                          | Short                       | Low                             |
| Herpes simplex              | Saliva, sexual       | 5–8                           | Long                        | Moderate                         |
| Enteroviruses               | Enteric, respiratory | 6–12                          | Long                        | Low                             |
| Poliomyelitis               | Enteric              | 5–20                          | Long                        | Low                             |
| Measles                     | Respiratory          | 9–12                          | Moderate                    | High                            |
| Smallpox                    | Respiratory          | 12–14                         | Moderate                    | High                            |
| Chickenpox                  | Respiratory          | 13–17                         | Moderate                    | Moderate                         |
| Mumps                       | Respiratory, saliva  | 16–20                         | Moderate                    | Moderate                         |
| Rubella                     | Respiratory, congenital | 17–20                      | Moderate                    | Moderate                         |
| Infectious mononucleosis    | Saliva, parenteral   | 30–50                         | Long                        | Low\(^d\)                       |
| Hepatitis A                 | Enteric              | 15–40                         | Long                        | Low\(^d\)                       |
| Hepatitis B                 | Parenteral, sexual, perinatal | 50–150                  | Very long                   | Low\(^d\)                       |
| Hepatitis C                 | Parenteral (perinatal, sexual) | 40–60                  | Very long                   | Low in acute infection          |
| Rabies                      | Animal bite          | 30–100                        | Nil                         | High                            |
| Warts                       | Contact, sexual      | 50–150                        | Long                        | High                            |
| HIV/AIDS                    | Sexual, parenteral, perinatal | 1–10 years              | Very long                   | High\(^e\)                      |
| SARS                        | Respiratory          | 2–10 days                     | Moderate                    | Moderate                         |

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\(^a\) Until first appearance of prodromal symptoms. Diagnostic signs, e.g., rash or paralysis, may not appear until 2–4 days later.

\(^b\) Most viral diseases are highly transmissible for a few days before symptoms appear, as well as after. Long, >10 days; short, <5 days.

\(^c\) High, >90%; low, <10%.

\(^d\) If acquired when young. Moderate if acquired as an adult, as occurs with higher socioeconomic conditions.

\(^e\) Eventually, after a long incubation period.
### TABLE 13.3 Non-Arthropod-Borne Viral Zoonoses

| Virus Family  | Virus                  | Reservoir Host          | Mode of Transmission to Humans |
|---------------|------------------------|-------------------------|--------------------------------|
| Herpesviridae | B virus                | Monkey                  | Animal bite                    |
| Papoviridae   | Cowpox virus           | Rodents, cats, cattle   | Contact, through abrasions     |
|               | Monkeypox virus        | Squirrel, monkeys       |                                |
|               | Pseudocowpox virus     | Cattle                  |                                |
|               | Orf virus              | Sheep, goats            |                                |
| Rhabdoviridae | Rabies virus           | Various mammals         | Animal bite, scratch, respiratory |
|               | Vesicular stomatitis   | Cattle                  | Contact with secretions*a      |
| Filoviridae   | Ebola, Marburg virus   | Fruit bats              | Human-human blood-borne contactb |
|               | Influenza A virus*c    | Birds, pigs             | Respiratory                     |
| Bunyaviridae  | Hantaviruses           | Rodents, birds          | Contact with rodent urine, feces |
| Arenaviridae  | Lymphocytic choriomeningitis, Junin, Machupo, Lassa viruses | Rodents, birds | Contact with rodent urine, feces |
| Paramyxovirida| Hendra, Nipah viruses  | Pteropid fruit bats     | Contact with infected horses (Hendra), pigs | Nipah)\(d\) |

*a May also be arthropod-borne.
*b Human outbreaks involve human-human spread, after initial introduction presumably from infected bats or amplifying infected primate species.
*c Usually maintained by human-to-human spread; zoonotic infections occur only rarely, but reassortants between human and avian influenza viruses (perhaps arising during coinfection of pigs) may result in human pandemics due to antigenic shift.
*d Human–human spread is also seen.

### TABLE 13.4 Major Arthropod-Borne Viral Zoonoses

| Virus Family  | Virus Genus | Disease                        | Reservoir Hosts          | Arthropod Vector¹ |
|---------------|-------------|--------------------------------|-------------------------|-------------------|
| Togaviridae   | Alphavirus  | Chikungunya                    | Monkeys, humans         | Mosquitoes        |
|               |             | Eastern equine encephalitis    | Birds                   |                   |
|               |             | Western equine encephalitis    | Birds                   |                   |
|               |             | Venezuelan equine encephalitis  | Mammals, horses         |                   |
|               |             | Ross River polyarthritis       | Macropods, other mammals|                   |
| Flaviviridae  | Flavivirus  | Japanese encephalitis          | Birds, pigs             | Mosquitoes        |
|               |             | St. Louis encephalitis         | Birds                   |                   |
|               |             | West Nile fever                | Birds                   |                   |
|               |             | Murray Valley encephalitis     | Birds                   |                   |
|               |             | Yellow feverb                  | Monkeys, humans         |                   |
|               |             | Denguec                        | Humans, monkeys         |                   |
|               |             | Zika                           | Humans, monkeys         |                   |
|               |             | Kyasanur Forest disease        | Mammals                 | Ticks             |
|               |             | Tick-borne encephalitis        | Mammals, birds          |                   |
| Bunyaviridae  | Phlebovirus  | Rift Valley fever              | Mammals                 | Mosquitoes        |
|               |             | Sandfly fever²                 | Mammals                 | Sandflies         |
| Nairovirus    |             | Crimean–Congo hemorrhagic fever| Mammals                 | Ticks             |
| Bunyavirus    | California encephalitis      | Rodents, rabbits           | Rodents, rabbits, hedges, | Mosquitoes        |
|               | La Crosse encephalitis       | Chipmunks, squirrels       | Hares, rabbits, hedges, | Mosquitoes        |
|               | Tahyna virus infection       | Rodents, rabbits           | Hares, rabbits, hedges, | Mosquitoes        |
|               | Oropouche fever              | Monkeys, birds, sloths     |                      | Mosquitoes, midges |
| Reoviridae    | Coltivirus  | Colorado tick fever            | Mammals                 | Ticks             |

¹Arbovirus transmission often requires a very specific insect species for a particular virus (see Part II for examples). On the other hand, if a transmission cycle changes to involve a different vertebrate host species, or to a different habitat (e.g., saltwater marshes or freshwater marshes), different insect species may then become involved.
²In certain episodes, transmitted from person to person, by insects.
³Usually transmitted from person to person, by mosquitoes.
**TABLE 13.5** Season of Maximal Incidence of Specifically Human Viral Infections in Temperate Climates

| Type of Infection       | Winter | Spring | Summer | Autumn | None in Particular |
|-------------------------|--------|--------|--------|--------|--------------------|
| **Respiratory**         |        |        |        |        |                    |
| Adenoviruses            | +      |        |        |        |                    |
| Rhinoviruses            | +      | +      |        |        |                    |
| Influenza               | +      |        |        |        |                    |
| Coronavirus             | +      |        |        |        |                    |
| Respiratory syncytial   | +      |        |        |        |                    |
| virus                   |        |        |        |        |                    |
| Parainfluenza 1 and 2   |        | +      |        |        |                    |
| Parainfluenza 3         | +      |        |        |        |                    |
| **Enteric**             |        |        |        |        |                    |
| Enteroviruses           |        |        |        |        | +                  |
| Rotaviruses             | +      |        |        |        |                    |
| Caliciviruses           |        |        |        |        | +                  |
| **Generalized**         |        |        |        |        |                    |
| Rubella                 |        | +      |        |        |                    |
| Measles                 |        |        |        | +      |                    |
| Mumps                   |        |        |        | +      |                    |
| Varicella               |        |        |        | +      |                    |
| Hepatitis B             |        |        |        |        | +                  |
| Herpes simplex 1 and 2  |        |        |        |        | +                  |
| Cytomegalovirus         |        |        |        |        | +                  |
| Epstein-Barr virus      |        |        |        |        | +                  |
| Most arboviruses        |        |        |        |        | +                  |

*Seasonality is often different in tropical climates, where there is little temperature fluctuation between summer and winter, but the occurrence of some infectious diseases is influenced by “wet” and “dry” seasons.*

**FIGURE 13.3** Epidemic occurrence of respiratory syncytial virus infections admitted to a children’s hospital in Buenos Aires between 2001 and 2013. Virological diagnosis was performed by indirect immunofluorescence using nasopharyngeal aspirates. Note the sharp clustering of cases occurring each southern hemisphere winter. Adapted from Lucion, M.F., et al., 2014, Arch. Argent. Pediatr. 112, 397–404.
Critical Community Size

The survival of viruses that produce acute self-limiting infections requires a large and relatively dense susceptible host population. Such viruses may disappear from a population if the potential supply of susceptible hosts becomes exhausted as individuals increasingly acquire immunity to reinfection. Persistent viruses, on the other hand, may survive in very small populations, sometimes by spanning generations. Depending on the duration of immunity and the pattern of virus shedding, the critical community size varies considerably with different viruses. The principle can be exemplified by a comparison of measles and chickenpox.

Measles is a cosmopolitan disease that is characteristic of the generalized viral infections of childhood, similar to rubella, mumps, and poliomyelitis. Persistence of the virus in a community depends on a continuous supply of susceptible subjects. With an incubation period of about 12 days, maximum viral excretion for the next six days, and solid immunity to reinfection, between 20 and 30 susceptible individuals would need to be infected in series to maintain transmission for a year. For a variety of reasons, nothing like such precise one-to-one transmission occurs, and thus many more than 30 susceptible persons are needed to maintain endemicity. Analyses of the incidence of measles in large cities and among island communities have shown that a population of about 500,000 persons is needed to ensure a large enough annual input of new susceptible individuals, provided by the annual birth cohort, to maintain measles indefinitely as an endemic disease. For this reason it is believed that measles is a relatively new infection of humans, as communities of this size would not have been present prior to the development of settled agrarian societies around 10,000 to 4000 BC.

Because infection depends on close contact, the duration of measles epidemics is inversely correlated with population density. If a population is dispersed over a large area, the rate of spread is reduced and the epidemic can last longer, and therefore the number of susceptible persons needed to maintain endemicity is reduced. On the other hand, in such a situation a break in the transmission cycle is much more likely. If a large proportion of the population is initially susceptible, the intensity of the epidemic builds very quickly.

Attack rates were almost 100% in an epidemic of measles in southern Greenland in 1951, spreading through the entire population in about 40 days before running out of susceptible individuals and disappearing completely (see Box 13.3). Such virgin-soil epidemics in isolated communities may have devastating consequences, likely more due to a high proportion of the community being affected, a lack of adequate medical care, and the disruption of social life, rather than to a higher level of genetic susceptibility of the people or an exceptionally virulent virus strain.

BOX 13.3 Measles Epidemic in Greenland

Until 1951 measles had not been seen in Greenland, mainly due to the relative isolation of the population and the slow transport from surrounding countries. However in April 1951, a Greenlandic seaman traveled home from Copenhagen after being in contact with someone in the prodromal phase of infection. Unfortunately in his case the incubation period was unusually long (19 days before appearance of the rash, longer than the duration of the voyage), and second, while in the prodromal phase of infection he took part in a dancing festival involving several hundred people. The resulting epidemic infected all but 5 of the 4262 theoretically susceptible individuals in southern Greenland, with a mortality of 1.8% (greatest in those over 55 years of age) and encephalitis in slightly more than 1 in 1000. Since then, epidemics have recurred in other parts of Greenland following further introductions.

Bech, V. Measles epidemics in Greenland. Am J Dis Child. 1962;103(3):252–253. doi:10.1001/archpedi.1962.02080020264013.

The peak age of incidence of measles depends on local conditions of population density and the chance of exposure. In large urban communities, before the days of vaccination, epidemics occurred every two to three years, exhausting the available susceptible cohort of children. Epidemics on a continental scale occurred annually in the United States and European countries. Although the newborn population (the birth cohort) provides the input of susceptibles each year, the age distribution of cases in unvaccinated communities is primarily that of children just entering school, with a peak of secondary cases at about two years of age through family contacts. The cyclical nature of measles outbreaks is determined by several variables, including the build-up of susceptibles, introduction of the virus, and environmental conditions that promote viral spread. Both the seasonality of infectivity (Table 13.5) and the occurrence of school holidays affect the epidemic pattern. Following the widespread introduction of immunization programs the epidemiology of measles has changed dramatically (see Chapter 26: Paramyxoviruses).

Although chickenpox is also an acute exanthem in which infection is followed by lifelong immunity to reinfection, it requires a dramatically smaller critical community size for indefinite persistence of the disease: less than 1000, compared with 500,000 for measles. This is because varicella virus causes a persistent infection (see below) that, after being latent for decades, may be reactivated and cause zoster (shingles) (see Chapter 17: Herpesviruses). Although zoster is not as infectious as chickenpox itself (secondary attack rates of 15%, compared to 70% for chickenpox), it can, in turn, produce a new cycle of chickenpox in susceptible children or grandchildren, often many decades after the source individual suffered his or her primary infection.
Effects of Immunity

Immunity acquired as a consequence of either prior infection or vaccination plays a vital role in the epidemiology of viral diseases. In most generalized infections, acquired immunity, manifested largely by circulating IgG antibody, appears to be lifelong. This occurs even in the absence of repeated sub-clinical infections, as evidenced by studies of measles and poliomyelitis in isolated populations. In a classic paper on measles in the Faroe Islands written in 1847, Peter Panum, a Danish physician, demonstrated that the attack rate was almost 100% among exposed susceptibles, but that immunity conferred by an attack of measles experienced during an epidemic 65 years earlier remained solid in spite of no further introduction of the virus to the islands in the interim.

The situation is different with viral infections that are localized to mucosal surfaces such as the respiratory tract, since mucosal immunity is relatively short-lived. A large number of serotypes of rhinoviruses and a few serotypes of both coronaviruses and enteroviruses can produce superficial infections of the upper respiratory tract. The seemingly endless succession of common colds suffered by urban communities reflects a series of minor epidemics, each caused by a different serotype of virus—or a different virus. Protection against reinfection is due mainly to antibodies in the nasal secretions, primarily IgA antibodies. Although short-lived type-specific immunity does occur, there is no intertypic cross-immunity, hence the convalescent individual is still susceptible to all other rhinoviruses or coronaviruses. Most persons contract between two and four colds each year. Shedding of most respiratory viruses is short-lived (three to seven days after the onset of symptoms), but rhinoviruses can show prolonged shedding of virus for up to three weeks, long after the acute symptoms have subsided.

Epidemiological observations within isolated human communities illustrate the need for a constant supply of susceptible subjects or antigenically novel viral serotypes to maintain respiratory diseases in nature, and repeated, often sub-clinical, infections are important in maintaining herd immunity. Explorers, for example, are notably free of respiratory illness during their sojourns in the Arctic and Antarctica, despite the freezing weather, but invariably contract severe colds upon establishing contact once more with other humans.

The more radical change known as antigenic shift, attributable to genetic reassortment in influenza A virus, occurs much less frequently than antigenic drift (attributable to small mutations) but often leads to widespread epidemics since there is no background population immunity to the new virus. As genetic reassortment can also occur in rotaviruses and there are rotaviruses affecting several animal hosts, antigenic shift may also occur with these viruses, although this appears to be infrequent.

Persistent Infections

Persistent viral infections (see Chapter 7: Pathogenesis of Virus Infections, and Chapter 8: Patterns of Infection), whether or not associated with episodes of clinical disease, provide an enhanced mechanism for perpetuation of viruses. Individuals with persistent infection may shed infectious virus intermittently or continuously (Table 13.6). In the extreme case, this can reintroduce virus into a population in which many individuals have been born since the last clinically apparent episode of disease (thus

| Virus Family       | Virus                        | Comments                                                                 |
|--------------------|------------------------------|--------------------------------------------------------------------------|
| Herpesviridae      | Epstein-Barr virus, cytomegalovirus, HHV6 | Intermittent shedding in saliva, genital secretions, milk                 |
|                    | Herpes simplex virus types 1 and 2 | Recurrent excretion in saliva, genital secretions, for years             |
|                    | Varicella-zoster virus       | Shed from zoster lesions many years later                                 |
| Adenoviridae       | All adenoviruses             | Intermittent excretion from throat and/or feces                          |
| Polyomaviridae     | BK, JC polyomaviruses        | Excreted in urine                                                        |
| Arenaviridae       | All arenaviruses             | In rodents, intermittent shedding in urine                               |
| Hepadnaviridae     | Hepatitis B virus            | Persistent viremia; shedding may occur in semen, saliva                  |
| Togaviridae        | Rubella virus                | Persistent only in congenitally infected children; excreted in urine      |
| Flaviviridae       | Hepatitis C virus            | Persistent viremia; shedding may occur in semen                          |
| Retroviridae       | Human immunodeficiency viruses | Persistent viremia, excretion in genital secretions for years            |
| Papillomaviridae   | Human papillomaviruses       | Shed from warts; latent genomes may persist after warts regress          |
is an immunologically naive population). This transmission pattern is important for the survival of herpesviruses in small populations (see above for varicella-zoster).

Persistence of infection, production of disease, and transmission of virus are not necessarily linked. Thus persistent arenavirus infections have little adverse effects on associated rodent reservoir hosts but are efficient in continuing the infection chain. On the other hand, the persistence of viruses in the central nervous system, as with measles virus in subacute sclerosing panencephalitis (SSPE), is lethal but of little epidemiological significance since no infectious virus is shed. It is reasonable to postulate that herpesviruses and retroviruses, so well adapted to lifelong persistence and transmission within small isolated populations, were among the important human viruses found in our hominid ancestors.

Involvement of Non-human Reservoirs

The regular re-introduction of infection from a non-human reservoir, as in the case of zoonoses, both assists the perpetuation of a virus in human populations and governs the distribution and extent of these infections. Examples include many arboviruses (which are discussed in more detail below), rabies, and hantaviruses. The extent of human infection depends on the degree of contact with the animal reservoir and the prevalence of infection in the reservoir. The existence, and possible extent, of an animal reservoir is of fundamental importance in considering plans for the regional elimination or global eradication of any human viral disease.

Arthropod Transmission

Arthropod transmission is ecologically the most complex of all virus transmission modes. The term arbovirus (arthropod-borne virus) refers to a virus whose life cycle involves alternating replication stages in a vertebrate host and in a blood-feeding arthropod (usually mosquitoes or ticks). “Arbovirus” is an epidemiologically based term that includes viruses of many different families sharing this common mode of spread. The arthropod vector acquires virus by feeding on the blood of a viremic animal or person. The ingested virus replicates, initially in the arthropod gut and then in the salivary gland, over several days (the extrinsic incubation period); this period varies with different viruses and is influenced by ambient temperature. Virions in the salivary secretions of the vector are injected into new vertebrate hosts when the arthropods subsequently take a blood meal. In addition to the above, there are also certain situations where arthropod transmission may occur mechanically by contamination of the insect’s biting parts (“flying pin”).

Diseases caused by arboviruses tend to fall into several distinct forms:

1. asymptomatic infection or a non-specific syndrome of malaise and fever;
2. encephalitis, usually diffuse, in contrast to the usual focal pattern of herpes simplex encephalitis;
3. a syndrome of fever, arthralgia, myalgia with or without rash, and;
4. hemorrhagic fever, with or without hepatitis and jaundice.

Symptomatic dengue virus infection usually involves fever, arthralgia, and rash, but severe dengue (formerly called dengue hemorrhagic fever or dengue shock syndrome) involves hemorrhagic manifestations, hypotension, and shock that may be fatal.

Arthropod transmission provides a way for a virus to cross species barriers, since the same arthropod may bite birds, reptiles, and mammals that rarely or never come into close contact with each other. Vertebrate reservoir hosts are usually wild mammals or birds, which generally sustain sub-clinical infections producing an ongoing vertebrate-arthropod-vertebrate cycle. Humans are rarely involved in this typical maintenance cycle (enzootic cycle), unless they venture into a site where contact occurs with the infected. However there are important exceptions—urban yellow fever and dengue—where human–arthropod–human cycles are the usual pattern. Another pattern involves spread of infection from the primary maintenance cycle in the wild, to a cycle involving an amplifying host (e.g., a domestic animal species and/or a different arthropod species) and finally to a human host (Fig. 13.4).

Transmission of some arboviruses from one vertebrate host to another can also occur by additional mechanisms not involving an arthropod. Thus, in central Europe a variety of small rodents and ticks are reservoir hosts of tick-borne encephalitis virus. Goats, cows, and sheep are incidental hosts and are sub-clinically infected via tick bites; however, they excrete virus in milk, and the drinking of virus-laden milk may infect new-born animals. Humans may be infected either by being bitten by a tick or by drinking unpasteurized milk from an infected animal (see Fig. 36.10).

In contrast to the arthropod, which carries the virus throughout its short life, infected vertebrates usually recover rapidly, eliminate the virus, and develop a lasting immunity to reinfection. To be an efficient reservoir host, the vertebrate must be abundant and have a rapid turnover rate, and after infection it must maintain a high level of viremia for an adequate period. In turn, to be an efficient vector the arthropod must (1) be easily infected even when feeding on vertebrate host with a low titered viremia (called a low infection threshold), (2) be supportive of virus replication to a titer sufficient to infect its next vertebrate victim, (3) be able to deliver virus from the productive infection in its...
salivary gland into its saliva and then into its vertebrate host’s blood/tissues, and (4) be able to continue this sequence for its lifespan without adverse pathological effects of the infection. The arthropod must also have a distribution pattern, a flight range, a longevity, and biting habits adapted to the habitat and behavior of its vertebrate host(s). Under these circumstances, the virus flourishes indefinitely in cycles of co-existence with vertebrate and arthropod hosts. Given the multiplicity of different parameters affecting transmission and survival, arboviruses can be vulnerable of dying out, but also capable of causing rapid large human epidemics in different circumstances.

Humans living in regions where a particular arbovirus is enzootic are vulnerable to infection. A proportion of those infected may suffer severe, even fatal disease. Visitors such as tourists, soldiers, or forest workers are at greater risk as, unlike the indigenous population, they will not have acquired immunity from sub-clinical infection in childhood. In tropical countries where the arthropod vector is plentiful year-round, the risk is always present and human disease is endemic (e.g., jungle yellow fever). In regions subject to monsoonal rains, epidemics of mosquito-borne diseases may occur toward the end of the wet season, for example, Japanese encephalitis in parts of Southeast Asia. In some temperate countries, and particularly in arid areas, human epidemics of mosquito-borne arbovirus disease occur following periods of exceptionally heavy rain.

A puzzle that has concerned many investigators has been to understand what happens to the viruses during the winter months in temperate climates when the arthropod vectors are inactive. One important mechanism for overwintering is transovarial transmission from one generation of arthropods to the next. Arthropods such as ticks have several larval stages, and this is necessarily associated with transstadial transmission (across stadia or life-stages). Transovarial infection occurs in most tick-borne arbovirus infections and is often sufficient to ensure survival of the virus independently of a cycle in vertebrates; as far as virus survival is concerned, vertebrate infection is only important in amplifying the population of infected ticks.

Other possible mechanisms for overwintering are still unproven or speculative. For example, hibernating vertebrates have been thought to play a role. In cold climates, bats and some small rodents, as well as snakes and frogs, hibernate...
Hepatitis B and C viruses, and to a lesser extent HIV, can also be transmitted by doctors, dentists, acupuncturists, tattooists, etc., and there is also a risk to attending staff and laboratory personnel, via needle stick and similar injuries. The risk of nosocomial transmission is exacerbated by the fact that infectious patients may congregate together in health-care facilities, and invasive procedures and blood exposure may occur. Understandably, health professionals exercise particular care to prevent such events.

Epidemiological Investigations
Definitions of Disease Activity: Incidence and Prevalence

The comparison of past disease experience, and expected future risk, in different populations is expressed in the form of rates, that is the number of events in a standard population size, for example 1000, 100,000, 1,000,000, etc. Two rates are widely used: incidence and prevalence.

In all cases the denominator (total number of persons at risk) may be general, that is the total population in a state or country, or it may be a specific cohort of individuals known to be susceptible or at risk. The latter is often equated with the number of persons in a specified population who lack antibodies to the virus of interest (“susceptibles”). In each situation it is imperative to be clear about the nature of the denominator. All rates may be affected by various attributes that distinguish one person from another: age, sex, genetic constitution, immune status, nutritional status, and various behavioral parameters. The most widely applicable attribute is age, which may be linked with immune status as well as various physiological variables.

The incidence, or attack rate, is a measure of the number of events over time, for example, per month or per year, and is especially useful for acute diseases of short duration. The denominator includes both the population size and time frame, and incidence rates are usually expressed as cases per standard population size (e.g., 100,000) per standard time (e.g., one year). It will be immediately apparent that two additional aspects are important. First, it is usually the case that not all members of a population are susceptible, for example because of prior infection leading to immunity. Thus, an incidence rate recorded in a total population may produce a lower figure than a more targeted incidence rate based on those who are truly susceptible. Second, with nearly all viruses, not all infected individuals develop clinical disease, and many infections go unrecognized. Thus the incidence rate of clinical disease is invariably lower than the incidence rate of total infections. The ratio of clinical to sub-clinical, or apparent, infections varies widely between different viruses. For example, measles infections are almost always clinically apparent, whereas less than 1% of those infected with encephalitogenic arboviruses or with polioviruses develop encephalitis or poliomyelitis, respectively (Table 13.2).
The proportion of a population becoming infected during the course of a season or a year may fluctuate considerably, depending on factors such as the season, changes in human behavior, emergence of a new virus strain, etc. The secondary attack rate, applied to comparable relatively closed groups like households or classrooms, is a useful measure of the “infectiousness” of viruses transmitted by aerosol or droplet spread. It is defined as the number of persons in contact with the primary or index case who become infected or ill within the maximum incubation period, expressed as a percentage of the total number of susceptible persons exposed to infection.

It is difficult to measure the incidence of chronic diseases, especially where the onset is insidious, and 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 a population divided by the size of that population. Prevalence is a snapshot of the frequency that prevails at a given time, and it is thus a function of both incidence and duration of the disease. It may be expressed as a percentage, or as number of cases per population unit, for example 100,000. Seroprevalence refers to the frequency of individuals with antibody to a particular virus in a population, and as neutralizing antibodies often last for many years, or even for life, seroprevalence rates usually represent the cumulative experience within a studied population.

Deaths 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), usually expressed per 100,000; or the case-fatality rate (the percentage of persons with a particular disease who die from the disease).

**Laboratory Approaches**

**Seroepidemiology**

Traditional surveillance is based on the reporting of clinical disease. However, examination of sera for antibodies gives a more accurate measure of the true prevalence of a particular virus in a given population. By detecting antiviral antibodies in various age groups it is possible to determine how effectively viruses have spread, or how long it has been since the last appearance of non-endemic viruses. Correlation of serological tests with clinical observations also makes it possible to determine the ratio of clinical to sub-clinical infections (Fig. 13.5).

Seroepidemiology is extremely useful in support of public health policy and research (Box 13.4). Advantage is often taken of a wide range of sources of human sera, such as prior population surveys, entrance examinations for military and other personnel, blood banks, hospitals, and public health laboratories. Such sera can be used in order to determine the prevalence of particular infections, to evaluate eradication and immunization programs, and to assess the impact, dynamics, and geographical distribution of new, emerging, and reemerging viruses. For example, serological surveys have been essential to determine the prevalence and geographical distribution of HIV, HBV, and HCV. More recently, concerns about the possibility of breaches of privacy have led to the

**FIGURE 13.5** (A) Seroepidemiology of Epstein-Barr infection in relation to socioeconomic conditions. The y-axis shows the prevalence of EBV antibody at different age groups in three different populations. Note, in developed countries with a high SE status, peak rates of transmission (steepest curve increases) correspond to <1 to 5-year-old and 15 to 25-year-old cohorts, the two ages where salivary contact is likely to be greatest. (B) Incidence of clinical cases of infectious mononucleosis at different age groups in three different studies. The relatively small number of cases of clinical disease in children is because infections in the young carry a low rate of clinical disease, while the decline in clinical cases in older age groups is because fewer new infections occurred in this age group. Modified from Fields, B.N., et al. (Eds.), 1996. Fields Virology. Lippincott-Raven, Philadelphia, PA.
imposition of constraints on the use of anonymous stored human sera as an epidemiological research resource.

Sentinel studies in animals are widely used for assessing the seasonal prevalence of arbovirus infections; for example, sentinel chickens are used for the early detection of eastern equine encephalitis and St. Louis encephalitis viruses in the southern United States and for the detection of Murray Valley encephalitis virus in Australia.

**Molecular Epidemiology**

Advances in rapid sequencing techniques (Chapter 10: Laboratory Diagnosis of Virus Diseases) have allowed the ready analysis and comparison of virus genome sequences to answer many epidemiological questions (Box 13.5). An excellent example is the use of partial genome sequencing in order to distinguish poliovirus vaccine strains from wild strains of poliovirus, and also to identify patient isolates containing one or more of the successive base changes that occur when each of the three vaccine strains progressively reverts to virulence. For many other viruses where different sequence variants are known to be endemic in different regions of the world, sequencing can identify the likely geographical origins of a new virus isolate. For example the strain of West Nile virus that first appeared in North America in 1999 was matched to a strain then circulating in Israel, suggesting the latter country as its likely source. The genome sequence of a rabies virus isolate from a human case is used to determine its geographical origin and reservoir animal species (Box 13.5).

Whenever an unusual cluster of cases occurs suggesting the appearance of a new or previously unrecognized virus, recovery of the virus and genome sequencing are done as soon as possible. From such information, the virus family, and often the genus, can be immediately identified by comparison with sequences in available databases. Occasionally it is possible to predict virulence attributes. Conversely, when a cluster of cases from around the same place or time are suspected of having a common source, sequence comparison between different samples can be used to ascertain whether the cases (and the suspected source) are linked epidemiologically, for example when successive patients attending a doctor’s surgery are later found to be HIV-positive and the question is raised whether or not this is due to iatrogenic transmission.

**Routine Surveillance**

The collection of accurate data about the occurrence of disease often requires considerable resources and ingenuity. Data on the population (denominator) are usually available, but it is difficult to obtain accurate information about the number of cases. Where such information is regarded as essential for public health purposes, cases may be notifiable by law. In practice, physicians tend not to be sufficiently conscientious about reporting, and of course some infected individuals do not consult a physician. To help overcome this problem, many public health authorities enlist selected practitioners into a network of “sentinel practices,” and
engage hospital and public health diagnostic laboratories to provide integrated information about clinical cases, virus identification, and serology. Local and international data on infectious diseases are available in electronic and printed formats in order to disseminate information and maintain the interest of both practitioners and laboratories, examples being the Morbidity and Mortality Weekly Report (MMWR) published by the Centers for Disease Control and Prevention (CDC) in the United States, and the Weekly Epidemiological Record of the World Health Organization (WHO). Public health departments of most governments also maintain websites containing information, advice, and warnings about recent and current infectious diseases (see also Chapter 14: Control, Prevention, and Eradication).

Special arrangements for surveillance are set up to address high-priority problems. For example, HIV/AIDS surveillance programs supported by national and international bodies provide detailed data. Other examples are the WHO influenza-reporting network aimed at rapidly identifying new epidemic strains of influenza. Yet another is the clinical/laboratory surveillance system for acute flaccid paralysis (AFP) that is an integral component of the global polio eradication campaign. WHO, and national public health authorities such as CDC in the United States, respond promptly to the occurrence of unusual outbreaks of disease by setting up special “task forces” of appropriately experienced epidemiologists and laboratory scientists including virologists and pathologists to investigate such problems. Recent examples include the investigation of severe acute respiratory syndrome (SARS) in 2003, H5N1 avian influenza (since 2003), and recurring outbreaks of Ebola virus disease in Uganda, South Sudan, the Democratic Republic of Congo, and the countries of West Africa.

**Cross-Sectional, Case-Control, Cohort, and Long-Term Population Studies**

A *cross-sectional study* to measure the prevalence of a given marker in a population can be carried out relatively quickly. One caveat is that populations are often not homogeneous; a small subgroup at high risk may contribute most of the cases, and a major determinant of prevalence in any one study may be the size of such a subgroup in the total sample. For instance, blood donors have long been a carefully selected group where individuals with risk factors for blood-borne diseases are excluded, and, depending on the thoroughness with which this exclusion is done, blood donors may not be representative of the general population. Age-specific prevalence rates go further and give considerable information about historical changes and mechanisms of virus transmission (Fig. 13.5).

A *case-control study* is initiated after the disease has occurred, the purpose being to identify the cause by comparing cases and controls. It is thus a retrospective study, going back in time to determine causative events; it requires careful selection of the control group, matched to the test group so as to avoid bias, together with careful selection of the questions and tests used. It can be used, for example, to answer whether a particular enteric virus can cause disease, by comparing the rate of excretion of the virus in a cohort of children hospitalized with gastroenteritis, with a group of age-matched children hospitalized for some other reason.

*Cohort studies*, usually carried out prospectively, start with a presumed cause or possible future risk, for example a new treatment or vaccine. A population exposed to infection is followed over time in order to identify significant correlates, such as outcome of disease, reinfection, vaccine efficacy, etc. This type of study requires the recording of new data, and the careful selection of a control group that is as similar as possible to the exposed group, except for the absence of contact with the presumed causative influence or treatment. Such studies do not lend themselves to rapid conclusions, as groups must be followed until disease is observed. Such studies are invariably expensive; however, successful cohort studies can provide strong evidence for cause–effect relationships and are essential for defining the safety of new vaccines. Long-term studies of families or larger groups, for example the population of a city, can yield much useful information about the natural history of diseases and the long-term effects of, for example, interventions, chronic infections, or environmental factors, but such studies are expensive and require long-term dedication of both personnel and resources.

The discovery as to the cause of congenital defects by rubella virus provides examples of both retrospective and prospective studies. Norman Gregg, an ophthalmologist working in Sydney, Australia, was struck by the large number of cases of congenital cataract he saw between 1940 and 1941, and by the fact that many of the children also had cardiac defects. By interviewing the mothers he found that the majority had experienced rubella early in pregnancy. His hypothesis that there was a causative relation between maternal rubella and congenital defects quickly received support from other retrospective studies, and prospective studies were then organized. Groups of pregnant women were sought who had experienced an acute exanthematous disease during pregnancy, and the subsequent occurrence of congenital defects among their children was compared with that among women who had not experienced such infections. Gregg’s predictions were thus confirmed and the epidemiology of congenital rubella syndrome more precisely defined.

**Human Volunteer Studies**

Many major discoveries that have led to the control of viral diseases were possible only with the use of human volunteers. Early work with yellow fever, viral hepatitis, the common
in new agent. Some of the approaches followed are outlined in new variant of a known virus, or a completely new one that for some reason has changed its characteristics or usual disease. These may involve a recognized virus infection frequently involved in investigating new outbreaks of disease. Epidemiologists, virologists, and other professionals are reducing the risk of secondary transmission to contacts.

Agents present in an inoculum as a contaminant; subjects assessed, including the possibility of transferring adventitious (IECs) and human subject committees (HSCs). It is essential that overgeneralizing predictions drawn from modeling has supported comprehensive studies of the epidemiology of the disease under study, the manner of its transmission, peak of infectiousness, and even if new variants are emerging as the outbreak progresses. Modeling in this way was invaluable in controlling the 2001 foot and mouth disease outbreak in the United Kingdom. Modeling has been the key in refining global guidelines for dealing with a smallpox bioterrorism event—three models have confirmed that large-scale ring vaccination using vaccines stores under WHO auspices would extinguish spread very quickly. Such methods proved useful also in predicting how monkeypox spread in the United States in 2003 and in understanding the reemergence of arthropod-borne diseases such as dengue.

As modeling has evolved in recent years, it has provided more and more insights that inform decisions regarding control. First, in some instances it has uncovered patterns in the evolution of an outbreak in terms of rate of spread and numbers of susceptible individuals likely to come into contact with the pathogen. This allows resources to be focused in such a way that an outbreak can be contained within the shortest period of time and the number of contacts is minimized. Second, in other instances modeling has allowed for a variety of control measures to be simulated and compared. Third, in yet other instances modeling has supported comprehensive studies of the epidemiology of the disease under study, the manner of its transmission, peak of infectiousness, and even if new variants are emerging as the outbreak progresses. Modeling in this way was invaluable in controlling the 2001 foot and mouth disease outbreak in the United Kingdom. Modeling has been the key in refining global guidelines for dealing with a smallpox bioterrorism event—three models have confirmed that large-scale ring vaccination using vaccines stores under WHO auspices would extinguish spread very quickly. Such methods proved useful also in predicting how monkeypox spread in the United States in 2003 and in understanding the reemergence of arthropod-borne diseases such as dengue.

As with all modeling approaches, it is essential both to be clear as to the questions being asked of the model and to take into account all known epidemiological data. Finally, it is essential that overgeneralizing predictions drawn from modeling, often by scholars not regularly involved in disease control, not be allowed to influence the public through the press or media nor influence political decision makers.

### Epidemiological Parameters

The following epidemiological parameters are required for modeling: the basic reproductive number ($R_0$), the degree of variation in infectivity between cases, the time for infections to take hold, and the duration of infectiousness.

**Box 13.6 Transmission of Hepatitis Viruses**

One notable study of hepatitis viruses was carried out by Saul Krugman and Joan Giles among children with intellectual disabilities in the Willowbrook State School on Staten Island in New York. Hepatitis infections were endemic in the 1960s among the institutionalized children despite all medical and nursing measures to prevent transmission. Krugman and Giles studied these infections, isolated two prototype infective sera that we now recognize contained hepatitis A and B respectively. Their work represented pioneering advances including defining the clinical characteristics of HAV and HBV infections, demonstrating that there were two distinct agents with no cross-protection, and ultimately demonstrating the feasibility of passive and active immunization against HBV. This work laid the foundation for HBV vaccine development. In subsequent years Krugman and Giles were severely criticized because this work was considered by many commentators as unethical. Krugman and Giles had gone to great lengths to obtain proper informed consent and had fully described their sensitivity to the interests of their subjects. It can now be said that the work was carried out in full accordance with the ethical standards and practices of the 1960s. However, given the ethical standards and regulatory practices of today, it can also be said that despite the importance of the subject and the results obtained, this work would not now be approved in any country with a human subjects regulatory system.

Cold, and a range of other respiratory infections involved human volunteers because of a lack of relevant animal models. An absolute requirement has been that investigators obtain informed consent from the subjects or, in the case of minors, from their parents (Box 13.6). In most countries today, human subject research is highly regulated by governmental agencies; at the heart of review and oversight are local institutional review boards (IRBs), also known as independent ethics committees (IECs) and human subject committees (HSCs). It is essential in such oversight that short- and long-term risks be carefully assessed, including the possibility of transferring adventitious agents present in an inoculum as a contaminant; subjects may need to be isolated for the duration of such studies, thus reducing the risk of secondary transmission to contacts.

### Outbreak Investigation

Epidemiologists, virologists, and other professionals are frequently involved in investigating new outbreaks of disease. These may involve a recognized virus infection that for some reason has changed its characteristics or usual prevalence or distribution; alternatively, it may potentially involve a new variant of a known virus, or a completely new agent. Some of the approaches followed are outlined in Chapter 15: Emerging Virus Diseases; this work includes some of the more challenging, glamorous, and sometimes dangerous roles for our profession.

### Mathematical Modeling

Ever since Daniel Bernoulli attempted in 1760 to model the likely effect of variolation on the spread of smallpox, there have been attempts to develop and refine mathematical models of disease transmission. Most of these studies have focused on identifying how single source, local outbreaks may be prevented from spreading, but the complexities of modern societies call for more models that recognize how individuals incubating emerging or unknown infections can quickly seed infections in multiple localities, for example as a result of air travel. Ease of air travel was the major determining factor in the spread of SARS virus to three continents in 2003 within days of the index case arriving in Hong Kong.

As modeling has evolved in recent years, it has provided more and more insights that inform decisions regarding control. First, in some instances it has uncovered patterns in the evolution of an outbreak in terms of rate of spread and numbers of susceptible individuals likely to come into contact with the pathogen. This allows resources to be focused in such a way that an outbreak can be contained within the shortest period of time and the number of contacts is minimized. Second, in other instances modeling has allowed for a variety of control measures to be simulated and compared. Third, in yet other instances modeling has supported comprehensive studies of the epidemiology of the disease under study, the manner of its transmission, peak of infectiousness, and even if new variants are emerging as the outbreak progresses. Modeling in this way was invaluable in controlling the 2001 foot and mouth disease outbreak in the United Kingdom. Modeling has been the key in refining global guidelines for dealing with a smallpox bioterrorism event—three models have confirmed that large-scale ring vaccination using vaccines stores under WHO auspices would extinguish spread very quickly. Such methods proved useful also in predicting how monkeypox spread in the United States in 2003 and in understanding the reemergence of arthropod-borne diseases such as dengue.

As with all modeling approaches, it is essential both to be clear as to the questions being asked of the model and to take into account all known epidemiological data. Finally, it is essential that overgeneralizing predictions drawn from modeling, often by scholars not regularly involved in disease control, not be allowed to influence the public through the press or media nor influence political decision makers.

### Epidemiological Parameters

The following epidemiological parameters are required for modeling: the basic reproductive number ($R_0$), the degree of variation in infectivity between cases, the time for infections to take hold, and the duration of infectiousness.
to recycle (the generation time, T), and the proportion of transmissions occurring before the onset of symptoms (θ).

The basic reproductive number \(R_0\) is an important parameter, representing the average number of secondary infections produced by an infected individual among a population of susceptible individuals. If the value of \(R_0\) is less than 1, then the chances of an infection generating new cases is insufficient for an outbreak to be maintained. If \(R_0\) exceeds 1, however, the number of secondary cases multiplies the infection and an epidemic ensues until the proportion of susceptible individuals declines. In cases where some of the population have pre-existing immunity, the effective reproduction number \(R\) is modified by applying a fraction representing this proportion of the population \((R = fR_0, with f representing the fraction of population susceptible to infection). Control measures look to reduce the value of \(R\) to below 1.

The value of \(R_0\) for a given virus in a given host population is determined by a number of different factors including the transmissibility of the virus, the period over which an infected host is infectious, the population density of hosts, and where appropriate, the density of relevant arthropod vectors and the capacity of such vectors to transmit the virus. The details of these relationships depend on the mode of transmission [e.g., direct contact transmission, indirect contact transmission (fomite transmission), sexual contact transmission, vector-borne transmission]. Equations used to calculate \(R_0\) have been developed which take into account the impact of life expectancy, duration of protection due to maternal antibody, the duration of protection afforded by a vaccine, etc. Many active immunization policies and programs take such calculations into account.

One of the difficulties with modeling is chance variation early in an epidemic. This was a particular difficulty in estimating the value of \(R_0\) during the SARS epidemic as a small number of individuals spread the virus to a disproportional greater number of secondary cases. Why this happened remains unclear, but it is known that some persons infected with other respiratory tract infections can shed larger than average amounts of virus. Importantly, this initial variation can be considerable, and greater variation can lead to more severe outbreaks. Fortunately, the value of \(R_0\) for SARS was around 3, somewhat more than for Ebola but considerably less than figures computed for smallpox and measles. Interestingly, SARS is also similar to smallpox in having a generation time (T) of approximately one week and \(\theta\) with a value of 0.11. The significance of this is that the quarantine and isolation of SARS cases were predicted as effective, as indeed was the case. Quarantine measures also have the benefit of allowing for more accurate estimates of \(\theta\) as the time from contact to onset of symptoms can be accurately defined.

Models have inherent difficulties in predicting just how large an epidemic will be. This in the main is due to the enormous difficulty in measuring how individuals interact with each other within their communities. Most models assume a uniform mix of people, each having the same probability as all others in terms of coming into contact with an infected person. This might be true at the local level, but becomes increasingly invalid as individuals move between communities, cities, and national boundaries. One individual may travel from one subpopulation to another, introducing the pathogen to a completely new population of susceptible individuals. In this case, the size of an outbreak is determined by the behaviors of a relatively small number of infected individuals. In the end, the final size of an epidemic and its duration is determined by the structure of the population as much as it is by \(R_0\), and estimates of epidemic size need to recognize a series of subpopulation structures through which an infected individual may pass. Therefore epidemics are the result of smaller local outbreaks within subpopulations where most transmission occurs, accompanied by much broader spreading by a small number of infected individuals: increasingly over the past 50 years, this process of seeding has been the result of long-distance air travel.

The usefulness of modeling is critically dependent upon accurate and rapid diagnosis of an infection within days of the first cases being recorded. Modeling shows that the effectiveness of control measures can fall off rapidly unless the correct control policy is implemented: crucially this can often be when variability of secondary transmission is greatest and statistical treatment of small case numbers least reliable. Once robust data are available, however, predictions as to the progression of an epidemic, its economic impact, and the likely consequences on healthcare resources can work wonders in galvanizing political support to ensure adequate resources are allocated.

**FURTHER READING**

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