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Abstract

Concepts required to understand the epidemiology and ecology of vector-borne diseases are presented in sections that cover components of the transmission cycle, modes of transmission by the vector, different types of transmission cycles based on vertebrate hosts, vector incrimination, interseasonal maintenance mechanisms, and surveillance. Minimal components required for transmission of a vector-borne pathogen include a competent vertebrate host and an arthropod vector, a virulent pathogen, and a suitable environment. The efficiency of transmission depends on the frequency of contact between host and vector and is delineated by blood meal acquisition behavior by the vector and environmental conditions that drive the system. Transmission cycles mostly have evolved from sylvan zoonoses comprised of a diverse variety of hosts and vectors to urbanized anthroponoses comprised of human hosts and a limited number of vectors that frequently rest and blood feed in houses. Vector incrimination is dependent upon the diagnosis of frequent field infection, degree of competent host contact, and vector competence determined experimentally. Many vector-borne pathogens appear to have evolved in the tropics, but have become a serious public, veterinary, or wildlife health problem after invading temperate latitudes. Here, interseasonal maintenance becomes a key element for pathogen persistence, delineates endemicity, and delimits distribution in time and space. Because outbreaks of vector-borne disease occur intermittently even in endemic areas, surveillance programs are required to track cases and the pathogen within transmission cycles in time and space to inform public health policy and provide operational decision support to direct intervention.

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2.1 Introduction

Epidemiology (etymology: epi=upon, demos=people, logos=study) developed as a science through the investigation of outbreaks of infectious diseases. As a modern discipline, it deals primarily with the natural history and spread of diseases within human and animal populations. Vector-borne diseases comprise a subset of infectious diseases and are caused by parasites that are transmitted by arthropods. The transmission cycle minimally consists of a competent arthropod vector, a susceptible vertebrate host, and a virulent parasite interacting within a favorable environment (Fig. 2.1). Where these factors come together in time and space is known as the *nidus* (literally nest or center) of infection (Pavloskiy 1966). The spread of parasites by arthropods is complex, because in addition to the myriad of interactions between the vertebrate host and the parasite to cause disease, an arthropod is required to distribute the parasite among uninfected hosts. The ecology, behavior, and

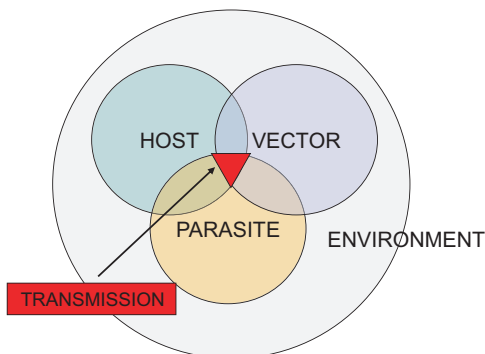


Fig. 2.1 Four required components of a vector-borne transmission cycle: (1) susceptible vertebrate host, (2) competent vector, (3) infectious parasite, and (4) suitable environment. Transmission occurs when all four components come together in time and space (Adapted from Reisen 2010)

physiology of the arthropod as well as environmental factors such as temperature and rainfall impact the transmission processes by affecting the rate of parasite acquisition and maturation within the arthropod host and distribution of the parasite to new hosts. Failure of any one of the basic cycle components may result in local parasite extinction.

With an epidemiological context, a *vector* is an arthropod responsible for distributing a parasite (not the disease) among vertebrate hosts. *Disease* is the response of the host to infection with the parasite. A *parasite* in this chapter is any organism, including viruses, bacteria, protozoa, helminths, and arthropods, which is dependent upon a host for its survival. Parasites may or may not cause disease. When a parasite injures its host and causes disease, it is referred to as a *pathogen*. A *vector-borne disease*, therefore, is an illness caused by a pathogen that is transmitted by an arthropod vector. *Facultative parasites* may have both free-living and parasitic forms, whereas *obligate parasites* are totally dependent upon their host(s) to provide their requisites for life. *Ectoparasites* live on or outside the host, whereas *endoparasites* live inside the host. When interacting with their hosts, ectoparasites produce an *infestation* that typically remains topical or peripheral, whereas endoparasites produce an *infection* when they invade host tissues or cells. The occurrence and severity of disease depend upon host–parasite interaction after infection and are often related to the immune response of the host. A host carrying a parasite is *infected*, whereas an infected host that is capable of transmitting a parasite is *infective* or *infectious*. A host capable of parasite maintenance without severe clinical symptoms is a *carrier*.

Understanding the epidemiology of arthropod-borne disease requires knowledge of the ecology, physiology, immunology, and genetics of parasite, arthropod vector, and vertebrate host populations

and how they interact within their environment. Although specific methods of investigation vary considerably among the vast array of vectors and vector-borne parasites, overarching concepts unify the information necessary to understand the epidemiology of vector-borne diseases. Information on the disease typically evolves chronologically from the discovery of the parasite as the causative agent to identifying its mode of transmission by the arthropod vector(s) among vertebrate hosts and to monitoring, forecasting, and intervention. During the discovery period, clinical case definition and diagnosis are established enabling the tracking of human and/or veterinary cases in time and space, and the causative agent is identified, leading to the development of specific laboratory diagnosis and perhaps indicating that an arthropod may be responsible for transmission. The incrimination of the vector(s) requires a combination of field and laboratory investigation that measures abundance in time and space, blood-feeding patterns, field infection rates, and vector competence. Although short-term studies rapidly may determine the mode(s) of transmission, delineating the components of transmission cycles and interseasonal maintenance mechanisms typically requires years of careful ecological investigation and laboratory experimentation. Effective surveillance and control programs are best implemented after maintenance, amplification and epidemic transmission patterns have been described. Practically, discovery rarely progresses in the orderly fashion outlined above, and frequently, monitoring and management of cases progress more rapidly than the discovery of the vector or the mode(s) of transmission.

The current chapter details, in a general sense, the mechanisms by which arthropods serve as vectors of parasites that cause human or veterinary diseases. Although some examples are presented, details of specific parasites and their vectors will be described by others in subsequent chapters. This chapter revises and updates a similar presentation (Reisen 2009) that was published in *Medical and Veterinary Entomology* (Mullen and Durden 2009). Some overlap and redundancy between chapters were unavoidable as many of the definitions and concepts have not changed.

2.2 Components of Transmission Cycles

The components of a *transmission cycle* of an arthropod-borne disease include (1) a parasite that can multiply within both vertebrate and invertebrate host tissues, (2) a vertebrate host (or hosts) which develops a level of infection with the parasite that is infectious to the vector, (3) a competent arthropod vector that is able to acquire the parasite from the infected host and is capable of transmission, and (4) a suitable environment (Fig. 2.1).

2.2.1 The Parasite

A wide variety of human and animal parasites exploit arthropods as a means of transmission, including multiple families of viruses, bacteria, protozoa, and helminths. Vector-borne parasites have by necessity evolved mechanisms for tolerating high constant body temperatures and for evading the complex responsive immune systems of vertebrate hosts, as well as for tolerating variable body temperatures and avoiding the very different innate immune mechanisms of arthropod vectors. In addition, the parasites must locate and replicate in very different target organs and then develop mechanisms for transmission either by producing stages in vertebrates that aggregate where vectors blood feed or in vectors that can be deposited or injected during blood feeding. Asexual parasites such as viruses and bacteria employ the same life form to infect both vertebrate and arthropod hosts, whereas more highly evolved parasites such as protozoa and helminths have very different life stages within their vertebrate and arthropod hosts. In addition, some asexual parasites such as the plague bacillus at times may bypass the arthropod host and be transmitted directly from one vertebrate host to another by aerosol droplets or contact.

Among sexually reproducing parasites, the host in which gametocyte union occurs is the *definitive host*, whereas the host in which asexual reproduction occurs is the *intermediate host*. Vertebrates or arthropods can serve as either

definitive or intermediate hosts, depending upon the life cycle of the parasite. For example, humans are the definitive host for the filarial worm, *Wuchereria bancrofti*, because adult male and female worms mate within the human lymphatic system, whereas the mosquito vector, *Culex quinquefasciatus*, is the intermediate host where larval worms develop and transform without reproduction. In contrast, humans are the intermediate host of the *Plasmodium* protozoan that causes malaria, because only asexual reproduction occurs in the human host; haploid gametocytes produced in the human host unite in the gut of the definitive *Anopheles* mosquito host, after which transformation and asexual reproduction occur in a series of events that eventually produces infectious sporozoites in the salivary gland.

Disease is the response of the host to infection with the parasite and can occur in either vertebrate or arthropod hosts. *Immunity* includes all properties of the host that confer resistance to infection and plays an important role in determining host suitability and the extent of disease or illness. Some species or individuals within species populations have *natural (or innate) immunity* and are refractory to infection. Innate immunity does not require that the host has previous contact with the parasite. For example, humans do not become infected with avian malaria parasites such as *Plasmodium relictum*, even though infective *Culex* mosquito vectors feed frequently on humans and probably transfer sporozoites. Conversely, mosquitoes do not become infected with measles or the AIDS viruses that infect humans, even though these viruses undoubtedly are ingested by mosquitoes blood feeding on viremic human hosts.

2.2.2 The Vertebrate Host

One or more *primary vertebrate hosts* are essential for the maintenance of parasite transmission, whereas *secondary* or *incidental hosts* are not essential and may or may not contribute to parasite amplification. *Amplification* refers to the general increase in the number of parasites present in a given area. An *amplifying host* increases

the number of parasites and theoretically then the number of infected vectors. Amplifying hosts often do not remain infected for long periods of time and may develop severe disease. A *reservoir or maintenance host* supports parasite development, remains infected for long periods, and serves as a source of vector infection, but usually does not develop acute disease (similar to the *carrier* defined above). Humans can be the primary, if not, the only, hosts in diseases called *anthroponoses* such as malaria or be incidental hosts in *zoonoses* such as West Nile virus (WNV) with the basic cycle involving birds or mammals (Fig. 2.2).

Attributes of a suitable vertebrate host include vector accessibility, parasite susceptibility, and parasite transmissibility.

2.2.2.1 Accessibility

The vertebrate host must be abundant and fed upon frequently by vectors. Seasonality, daily activity rhythms, and habitat selection determine availability in time and space to host-seeking or questing vectors. For example, in New Jersey, USA, the avian hosts of eastern equine encephalomyelitis virus (EEEV) generally begin nesting in wetlands coincidentally with the emergence of the first spring generation of the mosquito vector, *Culiseta melanura*, thereby bringing EEEV, susceptible avian hosts, and mosquito vectors together in time and space (Crans et al. 1994). Conversely, although many of winter resident sparrows are highly susceptible to WNV, they arrive and are present during winter when the vectors enter diapause/quiescence and therefore are not important in transmission (Reisen et al. 2010).

Diel activity patterns also may be critical. Certain vectors host-seek at night along flight paths delineated by landscape features and blood feed upon those host species that are found along those flight paths. Similarly, ticks quest on vegetation along certain trails, at a certain height, and at certain times of the day when they are most likely to contact a suitable host. Epidemics of vector-borne diseases frequently have been associated with increases in the accessibility of human hosts to vectors during wars, natural disasters, environmental changes, or human migrations.

Transmission cycles: role of humans

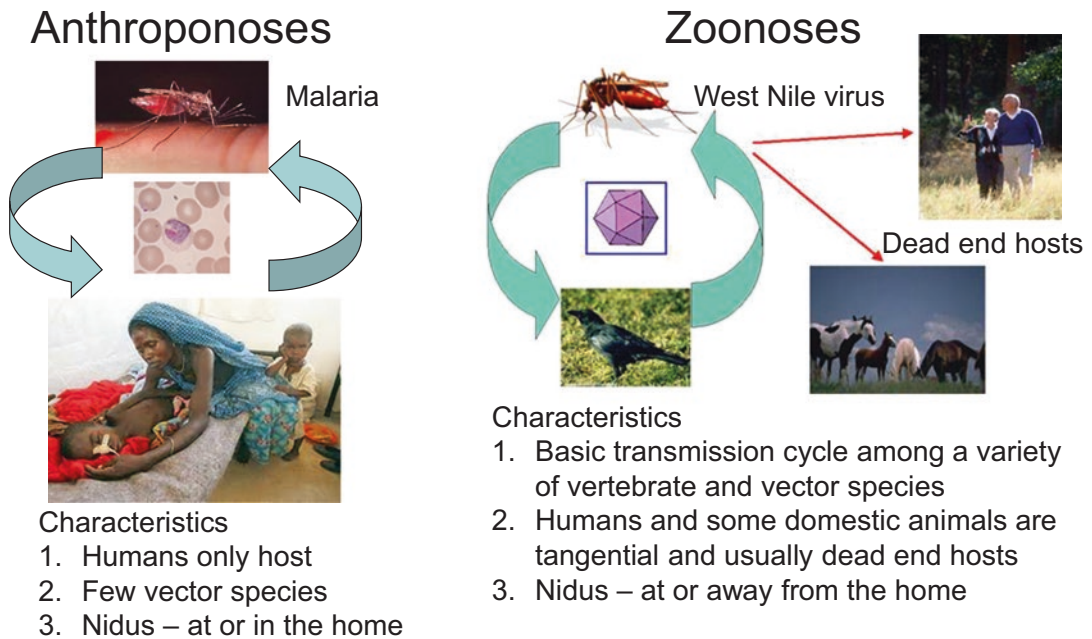


Fig. 2.2 Characteristics of anthroponosis and zoonosis transmission cycles using malaria and West Nile virus as respective examples (From Wikimedia)

For example, in 1952 a wet spring and flooding by the Kern River followed by a strong earthquake that destroyed most of the homes in Bakersfield, California, forced people to sleep out of doors and led to a large western equine encephalomyelitis virus epidemic (Reeves and Hammon 1962).

2.2.2.2 Susceptibility

Once exposed, a primary host must be susceptible to infection and permit the development and reproduction of the parasite. *Dead-end hosts* do not support a level of infection sufficient to infect vectors, although these hosts may become extremely ill and succumb. Ideal reservoir hosts permit parasites to survive in the peripheral circulatory system (or other suitable tissues) in adequate numbers for a sufficiently long time period to be an effective source for vector infection. Asexual parasites such as viruses and bacteria typically produce intensive infections that yield large numbers of infectious organisms for

relatively short periods during which the host either succumbs to infection or develops protective immunity. In the case of WNV, for example, 1 ml of blood from an infected American crow may contain as many as 10^{10} virus particles during both day and night for a 2–5-day period (Komar et al. 2003); birds that survive such infections typically develop long-lasting protective immunity. In contrast, highly evolved parasites produce comparatively few individuals during a longer period. *Wuchereria bancrofti*, for example, maintains comparatively few microfilariae in the blood stream (usually <10 microfilariae per ml of blood), which circulate most abundantly in the peripheral blood during periods of the day when the mosquito vectors blood feed (Weerasooriya et al. 1998). However, because both the worms and the human host are long lived, transmission is enhanced by repeated exposure rather than by an intense parasite presentation over a short period of time. In fact, infection with >25 microfilariae

per female mosquito may prove fatal, so limiting the number of parasites that infect the vector actually may increase the probability of transmission (Subramanian et al. 1998).

2.2.2.3 Transmissibility

Suitable numbers of susceptible vertebrate hosts must be available to become infected and thereby maintain the parasite population. Transmission rates typically decrease concurrently with a reduction in the number of susceptible (i.e., non-immune) individuals remaining in the host population. The *epidemic threshold* refers to the number of susceptible individuals required for epidemic transmission to occur, whereas the *endemic threshold* refers to the number of susceptibles required for parasite persistence. These numerical thresholds vary depending on the immunology and dynamics of infection in the host population and relate to the basic reproductive rate of the parasite, R_0 (May 1983). Therefore, suitable hosts must be abundant and either not develop lasting immunity or have a relatively high reproductive rate to ensure the rapid recruitment of susceptibles into the population. In the case of malaria, for example, the parasite elicits an immune response that rarely is completely protective, and the host remains susceptible to reinfection. In contrast, vector-borne virus infections of birds typically produce life-long protection, but bird life expectancy is short and the population replacement rate rapid, thereby ensuring the constant and rapid renewal of susceptible hosts.

2.2.2.4 Vertebrate Immunity

Some individuals infected with parasites recover and in the process acquire immunity. This acquired immunity ranges from transient to life long and may provide partial to complete protection. A partial immune response may permit continued infection, but may reduce the severity of disease, whereas a complete response results in parasite elimination and usually prevents reinfection. Acquired immunity may be humoral and result in the rapid formation of antibodies or may be cellular and result in the activation of T cells and macrophages.

Antibodies consist of five classes of proteins called *immunoglobulins* that have specific functions in host immunity. Immunoglobulin G (abbreviated IgG) is most common, comprising over 85 % of the immunoglobulins present in the sera of normal individuals. The IgGs are relatively small proteins, typically develop to high concentration several weeks after infection, and may persist at detectable and protective levels for years. Therefore, parasites such as yellow fever virus that induce long-lasting immunity are good candidates for vaccine development. In contrast, immunoglobulin M (IgM) is a large macroglobulin that appears shortly after infection, is very specific for the infecting parasite, but decays rapidly relative to IgG. For the laboratory diagnosis of many diseases, serum samples are tested during periods of acute illness and convalescence, 2–4 weeks later. The presence of elevated concentrations of IgM presumptively implies a current or very recent infection, whereas a fourfold or greater increase in parasite-specific IgG concentration in paired acute and convalescent sera provides confirmatory diagnosis. T cells and macrophages are several classes of cells that are responsible for the recognition and elimination of parasites. In long-lived vertebrate hosts, acquired immunity may decline over time, eventually allowing reinfection. Time here ranges from months in the case of human malaria to decades in the case of yellow fever virus.

Clinically, the host response to infection ranges from inapparent or asymptomatic to mildly symptomatic to acute. Generally it is beneficial for the parasite if the host tolerates infection and permits parasite reproduction and/or development without becoming severely ill and dying before vectors can be infected. However, the fitness of many parasites is contingent upon elevated virulence that causes high parasitemia and frequent mortality in the vertebrate host, but facilitates transmission by increased infection probability in the vector. Generally, the susceptibility of the vector to infection dictates the concentration levels or *virulence* of parasites required in the vertebrate host to infect vectors and complete the transmission cycle.

2.2.2.5 Risk Factors

A risk factor for human exposure is a variable statistically associated with an increased or decreased risk of disease and may depend on a variety of factors, including place of residence, socioeconomic status, occupation, age, and sex. Typically risk factors are correlational and frequently pathogen specific, closely interconnected, and studied as model covariates paired with serological or pathogen survey data. For vector-borne disease, risk may be related to frequency of exposure to the vector as well as innate susceptibility to pathogen infection and disease. Risk related to the place of residence varies with scale, pathogen endemicity, and vector exposure over coarse geographical areas delimited by landscape or political boundaries or over fine scale at microhabitat levels. For example, the USA is currently endemic for West Nile virus, whereas Brazil is not, whereas residents of houses within villages living close to mosquito larval habitat typically are at higher risk of pathogen transmission than houses furthest from these habitats. Socioeconomic status frequently is interrelated with residence, with poorer urban areas having higher risk of pathogen transmission due to inconsistent or no potable water delivery, open sewage drains, and poor solid waste management creating vector and rodent problems, and poor housing construction allowing vector access and harborage. Occupation often delimits the extent and type of exposure, related to time spent outdoors in wood gathering, agriculture or tending domestic animals, or spent indoors at the place of work or residence. The impact of age may be biased for exposure by occupation, but disease may be related to the response of the host to infection as well as exposure history. Even closely related pathogens may have markedly different age impacts which are poorly understood. For example, infection with Japanese encephalitis virus typically leads to neuroinvasive disease in children, whereas genetically related West Nile virus (WNV) most frequently expresses neuroinvasive disease in the elderly. Similarly sex-related disease risk is confounded by exposure as well as the response of the host to

infection. In many areas, men typically engage in outdoor activities such as entering forests for hunting or logging thereby exposing them to pathogens such as sylvan yellow fever virus cycling among forest mosquitoes and primates, whereas women may spend more time in and around the home thereby exposing them more frequently to diurnal endophagic mosquitoes such as *Aedes aegypti*¹ and dengue virus. In addition, certain hormones at high levels such as testosterone may serve as an immunosuppressant and facilitate more frequent disease in males.

2.2.3 The Arthropod Vector

Literally, a *vector* is a “carrier” of a parasite from one host to another. The degree of contact between the vertebrate host and vector ranges from intermittent (e.g., mosquitoes) to continuous (e.g., sucking lice). Frequently the host provides the vector not only food in the form of blood or other tissues but also a habitat or place in which to live such as a nest or burrow. Blood feeding by the vector is important, because it brings parasite, vector, and vertebrate host together in time and space and ultimately is responsible for the transmission of parasites from infectious to susceptible vertebrate hosts. The vector usually must take at least two blood meals during its lifetime to transmit a parasite, the first to acquire the infection and the second to transmit it. Blood meals are taken to provide the arthropod with nutrients necessary for reproduction as well as metabolism and metamorphosis. The *gonotrophic cycle*, or literally “reproductive feeding cycle” of the arthropod, includes the sequence of questing or searching for a vertebrate host, blood feeding, blood meal digestion, egg maturation, and oviposition. *Parous* females have completed one or more gonotrophic cycles and

¹Although several taxonomic modifications have been proposed on Culicidae genera, mostly splitting *Aedes* by Reinert et al. (2009) (and accepted by CBM), this taxonomy has been used in the chapters according to authors' preference. To facilitate utilization by health personnel, all new Aedine genera can be considered *Aedes* (CBM).

therefore have a greater probability of being infected with and transmitting parasites than *nul-liparous* females that have not reproduced and are host seeking or blood feeding for the first time. Unlike parasites that are transmitted directly from host to host, parasites transmitted by arthropods generally have replaced the free-living or environmentally resistant stages with those that can multiply and develop within the arthropod and be transmitted during the blood-feeding process.

An effective arthropod vector generally exhibits characteristics that complement those listed above for the vertebrate host and includes host selection, infection, and transmission.

2.2.3.1 Host Selection

Blood feeding by arthropods has arisen evolutionarily at least 21 times in different branches of the phylum Arthropoda and is the most important behavior for bringing vector, host, and parasite together in time and space. Most blood meals are used for extra protein and lipids for egg development, but they also can be used for water balance and nutrition (Clements 1992). An effective vector must be abundant and feed frequently upon infective vertebrate hosts when stages of the parasite are circulating in the peripheral blood stream or other tissues accessible to the vector. Difficulty in locating the vertebrate host depends upon the degree of intimacy and duration of contact and ranges from constant contact by ectoparasites such as sucking lice to intermittent contact by vectors such as mosquitoes that live away from the host. In the latter situation, the vector can either wait for the arrival of the host such as ticks questing by along animal trails or flea awaiting the arrival of the host at burrows or nests or alternatively search actively for the host as do female mosquitoes or flies. Patterns of host selection or encounter determine the types of parasites to which vectors are exposed. *Anthropophagic*² (literally “human-eating”) vectors such as some *Anopheles* mosquitoes feed selectively on humans and therefore are important

in the transmission of human parasites such as malaria (Fig. 2.2). Anthropophagic vectors which readily enter houses to feed on humans or to rest on the interior surfaces of the house are termed *endophilic* (literally, “inside loving”), whereas vectors which rarely enter houses are termed *exophilic* (i.e., “outside loving”). *Zoophagic* (“animal-eating”) vectors feed primarily on vertebrates other than humans, with *mammalophagic* vectors blood feeding primarily on mammals and important in the maintenance of mammalian parasites and *ornithophagic* vectors feeding primarily on avian hosts and important in the maintenance of avian parasites. Frequently host selection is dependent upon how diurnal rhythms and flight paths of questing vectors lead to encounters with available potential vertebrate hosts. Juxtaposition of landscape features, vector questing patterns, and vertebrate behavior enable these encounters (Reisen 2010).

2.2.3.2 Infection

To transmit the parasite, the vector must be able to penetrate the host skin, be susceptible to infection, and survive long enough for the parasite to complete multiplication and/or development to the infective stage. Not all arthropods that ingest parasites become infected or support parasite maturation, dissemination, and transmission. Usually infection of the vector is dose dependent and requires that the number of parasites ingested exceeds a minimal threshold. In addition, some arthropod species that are susceptible to infection under laboratory conditions seldom feed on vertebrate hosts infective with the parasite and/or survive long enough to allow parasite development in nature. *Aedes albopictus*, for example, readily becomes infected with WNV in the laboratory, but this mosquito is not considered an important vector in nature because it does feed consistently on birds, the primary host for WNV. The *transmission rate* is the number of new infections produced per unit of time and is dependent upon the frequency of blood feeding by the vector and the duration of the *extrinsic incubation period* or the time required for parasite development to the infective stage. Because arthropod vectors are poikilothermic, transmission rates frequently are

²The suffix “phagic” here has also been replaced by “philic,” meaning “loving” (CBM).

dependent upon ambient temperature and therefore proceed more rapidly at tropical than temperate latitudes and progress most rapidly during summer (Walton and Reisen 2014). The frequency of host contact and therefore the transmission rate also depend upon the life history of the vector. For example, epidemics of malaria in the tropics transmitted by an *Anopheles* mosquito that feeds at 2 day intervals progress faster than epidemics of Lyme disease at temperate latitudes where the spirochetes are transmitted to humans principally by the nymphal stage of the *Ixodes* tick vector that may have one generation and one blood meal per life stage per year.

2.2.3.3 Transmission

Once infected, the vector must exhibit a high probability of refeeding on one or more susceptible hosts to ensure the transmission of the parasite. Diversion of vectors to non-susceptible or “dead-end” hosts dampens transmission effectiveness. The term *zooprophylaxis* (literally, “animal protection”) originally described the diversion of host-seeking *Anopheles* infected with human malaria parasites from humans to cattle, a “dead-end” host for the malaria parasite. The dead-end host typically exhibits innate immunity where host tissues do not permit parasite growth to levels suitable to infect additional vectors. In some instances infection of the dead-end host results in serious illness, because the host–parasite relationship has not coevolved to the point of tolerance by the vertebrate host. WNV, for example, can cause serious illness in humans which are considered to be a dead-end host, because the virus rarely produces a viremia sufficient to infect mosquitoes. With zoonoses such as WNV in species diverse ecosystems, the *Culex* mosquito vector may blood feed on a wide assortment of avian hosts with a wide variety of competence thereby dampening amplification transmission, whereas in simple suburban/urban ecosystems with comparatively low avian diversity, *Culex* may blood feed on a limited number of competent hosts thereby enabling efficient transmission. Here, the loss in infective bites to dead-end hosts is called the *dilution effect* and is similar to zooprophylaxis.

2.2.3.4 Vector Immunity

After locating a suitable host, the skin, including hair and feathers, forms the first obstacle to blood meal acquisition by arthropods. This problem has been overcome by competent vectors with the coevolution of a varied assortment mouthparts designed to penetrate the skin and complex saliva that contains an assortment of analgesics to limit detection and anticoagulants, vasodilators, and antiplatelet-aggregating compounds to enhance tissue fluid and blood flow. As mentioned, not all vectors that ingest parasites with the blood meal become infected. Because arthropods typically are short-lived, they rely mostly upon genetically determined *innate immunity* to resist infection (Schmidt et al. 2008). Large parasites such as helminths may be destroyed by the cibarial armature during ingestion of the blood meal. Once in the midgut or *mesenteron*, the natural microbial flora may negatively impact parasites, limiting infection. However, the primary defense against most parasites seems to involve the midgut epithelium, where infections must be initiated prior to the formation of the *peritrophic* (literally, “around food”) *matrix* during blood digestion. Penetration of the epithelium involves receptor–ligand interactions, physical burrowing, or digestion of host cells. Response by the vector to these processes includes lytic and melanization events which reduce the number of parasites successfully entering the body cavity or *hemocoel*. Unless the epithelium has been compromised, viruses multiply within focal infections of mesenteron cells before escaping into the hemocoel (Hardy et al. 1983). Bacteria and some parasites either remain within the digestive tract (plague bacillus/*Leishmania*) or enter the hemocoel (*Borrelia* spirochete/malaria). In the hemocoel, parasites enter the open circulatory system, but then must evade *hemocytes* (several types of blood cells, including mostly granulocytes) that upon recognition of parasites respond by phagocytosis, encapsulation/melanization, and/or the secretion of immune factors. Transmission of most parasites depends on infection of the salivary glands and then injection with the saliva into the host during blood feeding. Some mosquitoes have salivary gland infection and escape barriers for some

World map of Köppen-Geiger climate classification

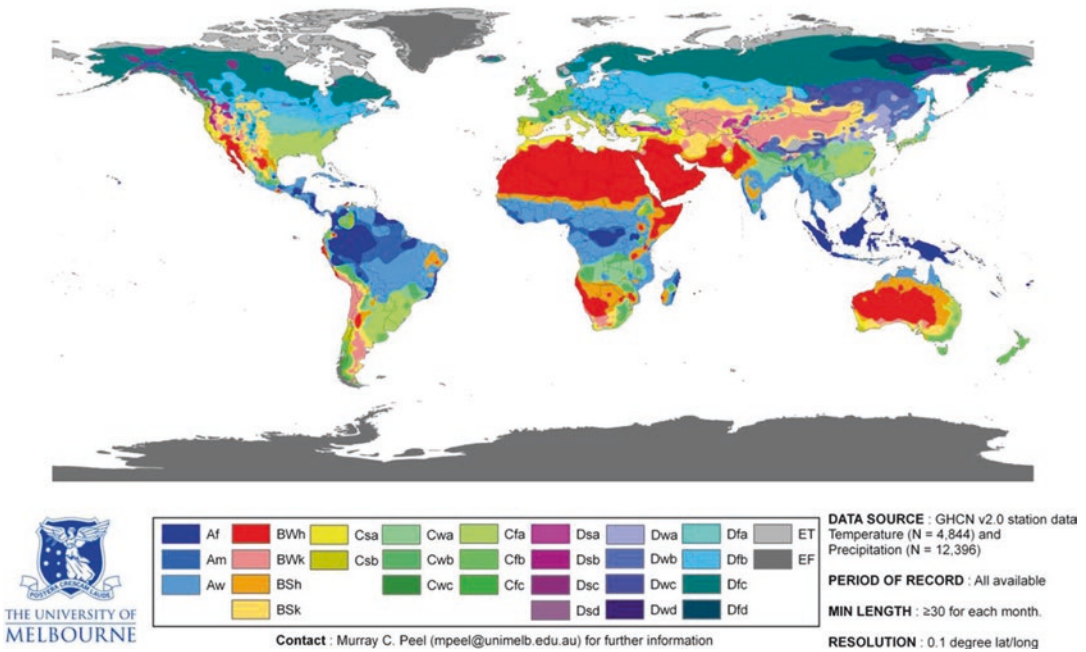


Fig. 2.3 Köppen–Geiger global climate classification (Downloaded from <http://people.eng.unimelb.edu.au/mpeel/koppen.html>; reference: Peel MC, Finlayson BS,

and McMahon. 2007. Updated world map of the Köppen–Geiger climate classification. *Hydrol. Earth Syst. Sci.* 11: 1633–1644)

arboviruses thereby blocking transmission, but these mechanisms remain poorly understood.

2.2.4 The Environment

In an epidemiological context, the environment includes all things surrounding the transmission cycle, including climate, habitat, and plant and animal communities (Reisen 2010). Climate³ is based on long-term patterns of temperature and rainfall and can be classified globally using schemes such as the Köppen–Geiger system based partly on the response of plant communities to temperature, moisture, soil, and slope (Fig. 2.3). Plant communities, in turn, delineate spatial suitability and often the distribution of vertebrate hosts, vectors, and their parasites.

Climate and the epidemiological environment are dynamic, with short-, mid-, and long-term variations, cycles, and trends imposed upon annual seasonality. In general, seasonal extremes between hot and cold increase as a function of latitude and/or elevation. Short-term climate variations in terms of days or weeks essentially define *weather* and include changes due to the interaction of global forces such as the jet stream modified by local landscape features such as oceans, mountains, and lakes. In recent years, scientists have recognized the importance of mid-term cycles in sea surface temperature on weather patterns. The Walker oscillation in the Pacific Ocean has been most intensively studied. Its cyclic variations are driven by interactions between the sea surface temperatures and the depth of the thermocline in the eastern Pacific off the western coast of North America (Fig. 2.4). The resulting *El Niño/Southern Oscillation* has multiyear cycles that strongly influence the distribution of the upwelling of warm moist air to

³More information on the influence of climate on diseases may be found in Chap. 37 (Geoprocessing) (CBM).

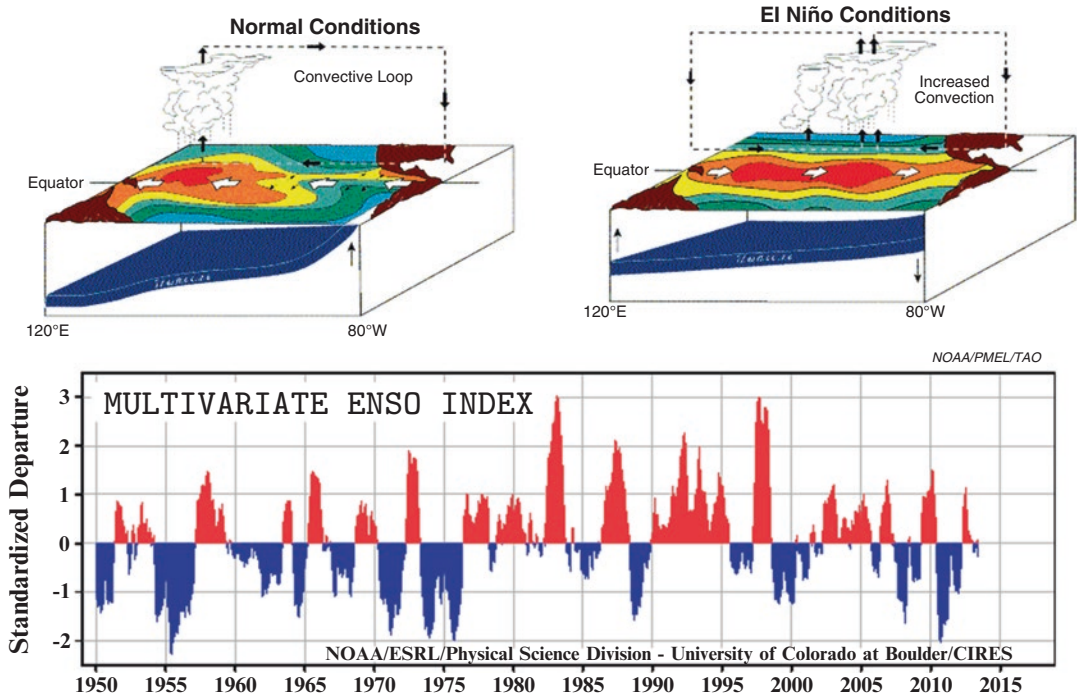


Fig. 2.4 Walker oscillation showing the upwelling of rain clouds during normal and El Niño conditions and time series changes in the ENSO index anomalies for the

Pacific. (Graphics downloaded from the US Climate Prediction Center, http://www.cpc.ncep.noaa.gov/products/analysis_monitoring/ensocycle/enso_cycle.shtml)

form rain clouds and subsequently temperature and rainfall patterns in the Pacific and the New World as well as the Indian Ocean and parts of eastern Africa. These oscillations and the resulting temperature and rainfall anomalies have a strong, but spatially variable, influence on vector and host populations and their parasites. In the central prairies of North America, for example, the incidence of human infection with WNV is linked closely with hot and dry summers (Reisen et al. 2006), whereas outbreaks of Rift Valley fever virus in Kenya are linked to above-normal rainfall, both associated with El Niño events (Linthicum et al. 1999).

Superimposed on short-, annual, and mid-term variations are long-term trends such as *global warming*. Linked closely to the dramatic increase in the earth's human population has been the expanding need for resources for fuel, housing, and food (O'Neill et al. 2010). Carbon-based fuel consumption, whether a dung cooking fire in a developing country or a jet engine airplane,

releases carbon dioxide and other chemicals into the air cumulatively creating a “greenhouse” effect that is gradually warming the earth. On a global scale, warming has varied spatially, being most dramatic at northern latitudes, where it has led to melting of the polar and Greenland ice caps and montane glaciers. Warming temperatures and changing rainfall patterns have altered the receptivity of these areas to vector-borne diseases due to milder and shorter winters and longer and warmer transmission seasons, leading to range extensions by vector species and outbreaks in susceptible populations. Examples include the invasion of Canada and the northern USA by WNV (Brault and Reisen 2014) and the African highlands by falciparum malaria (Chaves and Koenraadt 2010), both pathogens of tropical origin now creating outbreaks at new latitudes and elevations, respectively. In combination with anthropogenic changes such as urbanization, deforestation, and expansion of agroecosystems, vectors and parasites have extended their distributions, leading to

the emergence of new public health problems (Brault and Reisen 2014).

By definition, an *emerging disease* has shown a significant increase in incidence, severity, and/or distribution within recent history and threatens to remain or increase as a health problem in the future. Historically, human movement frequently has led to changes in pathogen distributions and public health. Expanding trade with Asia along the Silk Road during the 1300s, for example, was followed by plague epidemics which killed 30–60% of the European population (Kupferschmidt 1993). Recently, an expanding human population, an increased rapid travel, the globalization of commerce, and a variety of anthropogenic factors, including global warming and urbanization, have produced conditions conducive for the emergence and/or resurgence of new as well as old infectious diseases, including those transmitted by vectors (Institute of Medicine 2003). For many emerging diseases, a cascade of historical events altering human demography, vector or pathogen distributions, anthropogenic environmental change, and/or the genetics of the parasites have enabled the emergence of parasites, leading to major human, domestic animal, or wildlife health problems.

2.2.4.1 Human Demography

Although the global per capita population growth or birth rate has slowed in recent years, the earth's human population continues to increase at a constant rate and has tripled during the last generation. Demographers project final stabilization of the earth's human population at 10–12 billion or almost a 30–40% increase above the 7.5 billion realized in 2012. Per capita growth rates have been variable, with countries in Europe showing declines, whereas others in Africa showing marked increases. Growth rates frequently are linked to socioeconomic factors and childhood mortality. The transition from high birth–high death rate to low birth–low death rate changes population age structure and therefore the population receptivity to some vector-borne diseases that exert a greater health burden on young or old age groups. In addition, since 2012 more than 50% of the human population now resides in

rapidly expanding cities, where municipal services such as piped water and sewage have not kept abreast with growth. These conditions are especially conducive for the establishment of large *peridomestic* (living in or around human habitations) vertebrate and vector populations making them receptive for the introduction of new vectors and parasites. More humans living in close proximity linked by rapid travel has enabled the rapid transit of parasites, especially anthroponoses utilizing humans as reservoir or amplifying host. Historically, the large-scale displacement of ethnic groups or trade has created patterns of frequent and repeated travel that may be exploited by vectors and pathogens (Tatem 2009).

2.2.4.2 Globalization of Commerce

The globalization of commerce, originally by the sailing ships of the European colonial era and recently by rapid international exchange of goods by both sea and air, has established conditions suitable for the inadvertent transport of both vectors and the parasites they transmit. *Aedes aegypti* and *Ae. albopictus*, for example, both lay drought-resistant eggs in dark areas such as water barrels or tires that collect rainwater, enabling the transport of the immature stages, the circumglobal establishment of these effective arbovirus vectors, and an ongoing dengue virus pandemic of global proportions. Of additional concern is the wide-scale, and often illegal, trade in exotic pets that may bring with them parasites that may escape into new geographical areas.

2.2.4.3 Anthropogenic Change

A rapidly expanding human population and its growing need for food, fuel, and shelter have markedly altered the environment in ways conducive to the increase of vector-borne pathogens. The large-scale movement of the rural poor to urban centers to find jobs in developing countries and an unchecked human population growth have caused the large-scale unplanned *urbanization* in previously agrarian societies, the overwhelming of municipal infrastructure, the creation of inadequate housing, a lack of potable water that frequently must be stored for domestic use, and an absence of adequate waste management systems.

This has created conditions suitable for the increased abundance and distribution of peridomestic mosquitoes such as *Ae. aegypti* and the *Culex pipiens* complex that preferentially rest in houses and feed on humans (Gubler and Meltzer 1999). The reduction of species diversity and the increase of successful peridomestic commensals such as crows and house sparrows have enabled the highly efficient urban transmission of zoonoses such as WNV by *Cx. pipiens* complex mosquitoes (Brault and Reisen 2014). Ecosystem simplification by agriculture and urbanization has made parasite amplification more rapid and transmission more efficient than in complexylvan ecosystems, because there is less diversion of pathogens to noncompetent vertebrate or invertebrate hosts (Bonds et al. 2012). Some pathogens such as dengue and yellow fever viruses have transitioned from tropical zoonoses to anthroponoses and become *urbanized* (Weaver and Reisen 2010). Yellow fever virus, for example, persists naturally in the gallery forests of Africa and South America in cycles involving canopy primates and mosquitoes. When humans enter the forest or when primates raid invading agriculture, the virus transitions from canopy to village ecosystems where it is transmitted among humans by peridomestic *Ae. aegypti*. Human travel brings the virus to an urban *Ae. aegypti*—human transmission cycle—and the virus becomes urbanized, i.e., persists in the urban environment. Urbanization of viruses requires the presence of large human populations, because infection produces lasting immunity and therefore the continued need for nonimmunes for transmission to be maintained.

An *ecotone* is the transition area between biomes or landscapes dominated by different ecosystems and may appear as a gradual blending or a sharply delineated boundary. The alteration of landscapes and the spatial expansion of human and associated domestic animal populations into or adjacent to natural areas have concurrently expanded ecotone habitat and enabled the expansion of some zoonoses. Movement of housing into wooded areas of the NE USA, for example, has increased the forest ecotone; expanded browse vegetation thereby increasing

deer, mice, and associated tick vector populations; and produced the ongoing and expanding Lyme disease epidemic (Brownstein et al. 2005).

2.3 Modes of Transmission

The transmission of parasites by vectors may be either vertical or horizontal. *Vertical transmission* is the passage of parasites directly to subsequent life stages or generations within the vector population. Some vertical transmission systems may require a blood meal to trigger molting by the arthropod, but the host is not required for the infection process of the next stage. *Horizontal transmission* describes the passage of parasites between vector and vertebrate hosts and can be accomplished by vertically infected arthropods.

2.3.1 Vertical Transmission

Three types of vertical transmission are possible within vector populations: transstadial, transgenerational, and venereal.

2.3.1.1 Transstadial Transmission

Transstadial transmission (literally, across “stadia or stages”) is the sequential passage of parasites acquired during one life stage through the molt to the next stage(s) or stadium. Transstadial transmission is essential for the survival of parasites transmitted by mites and hard ticks that blood feed once during each life stage and die after oviposition. Lyme disease spirochetes, for example, that are acquired by larval ticks must be passed transstadially to the nymphal stage before they can be transmitted to other vertebrates.

2.3.1.2 Transgenerational Transmission

Transgenerational transmission (across generations) is the passage of parasites by an infected parent to its offspring in the next generation. Some parasites may be maintained transgenerationally for multiple generations, whereas others require horizontal transmission during each generation for amplification. Transgenerational transmission normally occurs *transovarially*

Modes of Transmission: LaCrosse encephalitis virus

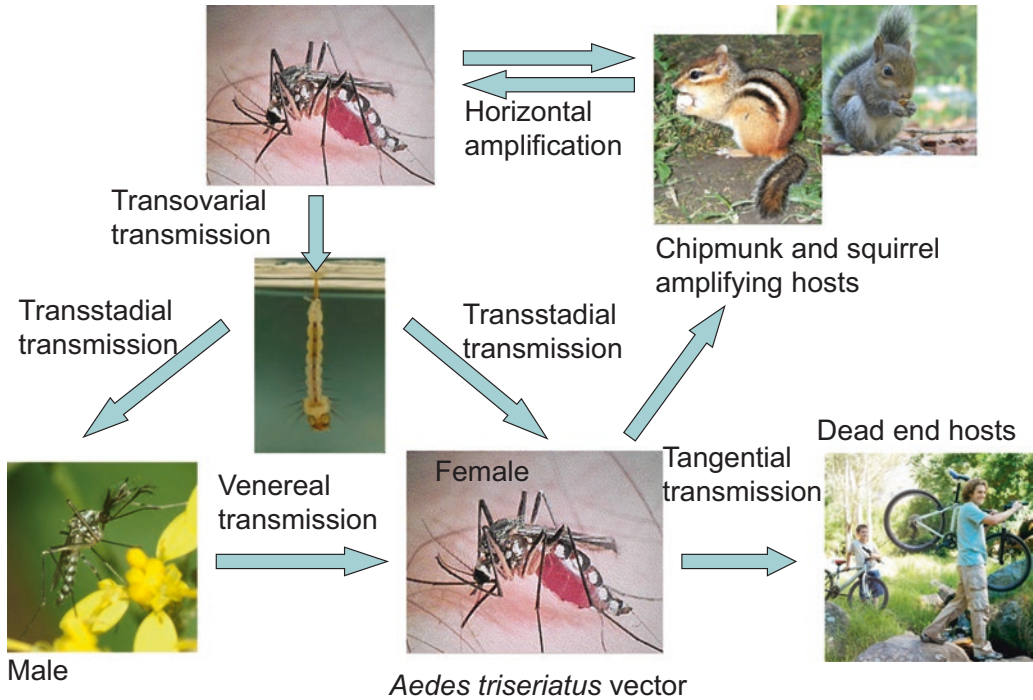


Fig. 2.5 La Crosse encephalitis virus transmission, showing multiple modes of transmission

(across the ovary) after the parasites infect the ovarian germinal tissue and then transstadially to the next reproductive or blood-feeding stage. In true transovarial transmission, most of the progenies are infected. Other parasites do not actually infect the ovary, and, although they are passed on to progeny, transmission is vertical but not truly transovarial. This latter situation is less efficient and usually only a small percentage of the progenies are infected. Transgenerational transmission in vectors such as mosquitoes also must include transstadial transmission, because the immature life stages do not blood feed.

2.3.1.3 Venereal Transmission

Venereal transmission is the passage of parasites between males and females of vector species during mating and is relatively rare. Venereal transmission usually is limited to transovarially infected males who infect females

during insemination which, in turn, infect their progeny during fertilization.

La Crosse virus (Fig. 2.5) is an example of a vertically maintained parasite where the arthropod host serves as the reservoir and the vector (DeFoliart 1983). This arbovirus is maintained transovarially by transgenerational transmission within clones of infected *Aedes triseriatus* mosquitoes in the eastern USA and is amplified by horizontal transmission among squirrels and chipmunks. Because this temperate mosquito rarely has more than two generations per year, the virus spends long periods in infected vectors and relatively short periods in infected vertebrate hosts. Female mosquitoes infected vertically or horizontally transmit their infection transovarially to first-instar larvae. These larvae pass virus transstadially through the four larval stadia and the pupal stage to emerging adults. These transgenerationally infected females then take a blood

meal and oviposit infected eggs, often in the same tree hole from which they emerged. Some blood meal hosts such as chipmunks become highly viremic and amplify the number of infected *Ae. triseriatus* when uninfected females feeding on these rodents become horizontally infected. Venereal transmission of virus from transgenerationally infected males to uninfected females has been demonstrated in the laboratory and may serve to establish new clones of infected females in nature. In contrast, scrub typhus rickettsia (*Orientia tsutsugamushi*) is vertically maintained transgenerationally within infected clones of the chigger mite *Leptotrombidium* and is transmitted to vertebrate hosts by bite of the larval stage; however, it has not been possible to experimentally establish new infectious colonies of mites in the laboratory by blood feeding (Frances 2005).

2.3.2 Horizontal Transmission

Horizontal transmission is essential for the maintenance of almost all vector-borne parasites and is accomplished by either anterior (biting) or posterior (defecation) routes. *Anterior-station transmission* occurs when parasites are liberated from the mouthparts or salivary glands during blood feeding (e.g., malaria parasites, encephalitis viruses, filarial worms). *Posterior-station (or stercorarian) transmission* occurs when parasites remain within the gut and are transmitted via contaminated feces. The trypanosome protozoan that causes Chagas' disease, for example, develops to the infective stage within the hindgut and is discharged onto the host skin when the triatomine bug vector *Rhodnius* defecates during blood feeding. Irritation resulting from salivary proteins introduced into the host during feeding causes the host to scratch the bite and rub the parasite into the wound. Louse-borne relapsing fever and typhus fever rickettsia also employ similar posterior-station modes of transmission.

There are four types of horizontal transmission, depending upon the role of the arthropod in the life cycle of the parasite: mechanical, multiplicative, developmental, and cyclodevelopmental.

Mechanical transmission occurs when the parasite is transmitted to vertebrate hosts without amplification or development within the vector, usually by blood feeding with contaminated mouthparts. Arthropods that are associated intimately with their vertebrate hosts and feed at frequent intervals have a greater probability of transmitting parasites mechanically. The role of the arthropod, therefore, may be little more than an extension of contact transmission between vertebrate hosts (Lindsay and Scudder 1956). Eye gnats (genus *Hippelates*), for example, have rasping, sponging mouthparts and feed at the mucous membranes of a variety of vertebrate hosts making them an effective mechanical vector of the bacteria and viruses which cause conjunctivitis or "pink eye." Pink eye also may be transmitted from infected to susceptible hosts by direct contact. Mechanical transmission also may be accomplished by contaminated mouthparts if the vector is interrupted while blood feeding and then immediately refeeds on a second host in an attempt to complete the blood meal. *Nonviremic transmission* is a special form of nonpropagative transmission where infectious vectors are able to transmit viruses through the host directly to concurrently feeding uninfected vectors without host infection or parasite replication. With *Ixodes ricinus* ticks, this occurs through the skin with viruses such as tick-borne encephalitis virus when multiple ticks feed adjacent to one another (Labuda et al. 1993). With mosquitoes, this has been demonstrated experimentally for WNV when infectious *Culex* vectors inject large quantities of virus directly into the circulatory system of small vertebrate hosts such as laboratory mice or house finches, and uninfected vectors feed concurrently or shortly after this initial feed (Higgs et al. 2005).

Multiplicative (or propagative) transmission occurs after the parasite multiplies asexually within the vector and is transmitted after a suitable incubation period is completed, allowing the parasite to disseminate to the salivary glands. In this case, the parasite does not undergo *metamorphosis* (transformation or development), and the form transmitted is indistinguishable from the form ingested with the blood meal. Arboviruses

such as dengue virus, for example, are not transmitted until the virus replicates within and passes through the mosquito vector midgut, is disseminated throughout the hemocoel, and then enters and replicates within the salivary glands. The number, but not the form, of the viruses changes during these processes, and the number of virus particles transmitted may be less than the number ingested with the blood meal. Likewise the titer of virus required to infect the vertebrate host typically is far less than required to infect the vector.

Developmental transmission occurs after parasite metamorphosis, but not multiplication, within the vector. Microfilariae of *Wuchereria bancrofti*, for example, are ingested with the blood meal, penetrate the mosquito gut, move to the flight muscles where they molt twice, and then move to the mouthparts where they remain until deposited on the skin during blood feeding. These worms do not reproduce asexually within the mosquito vector; i.e., the number of worms available for transmission is always equal to or less than the number ingested.

Cyclodevelopmental transmission occurs when the parasite metamorphoses and reproduces within the arthropod vector. In the life cycle of the malaria parasite, for example, haploid gametocytes that are ingested by the *Anopheles* mosquito vector with the blood meal unite within the mosquito midgut and then change to an invasive form (ookinete) that penetrates the gut and forms an asexually reproducing stage (oocyst) on the outside of the gut wall. Following replication, the oocyst ruptures and liberates the infective forms (sporozoites) that move through the hemocoel to the salivary glands from where they are transmitted when the mosquito vector expectorates during a subsequent blood meal.

The *extrinsic incubation period* is the time interval between vector infection and parasite transmission and originally was recognized by the time period between clinical cases when the parasite was “away” from the vertebrate host. The *intrinsic incubation period* is the time from infection to the onset of symptoms (or infectiousness) in the vertebrate host. Repeated lag periods of consistent duration between clusters of new

cases at the onset of epidemics were noticed by early epidemiologists who coined the term “extrinsic incubation.” These intervals actually represent the combined duration of extrinsic and intrinsic incubation periods.

The duration of the extrinsic incubation period in the arthropod is temperature dependent (Walton and Reisen 2014). The rate (or inverse of the time from infection to transmission) increases as a linear function of ambient temperature above a minimal threshold. After being ingested by the mosquito vector, arboviruses such as WNV, for example, must enter and multiply in cells of the midgut, escape the gut, be disseminated throughout the hemocoel, and then infect the salivary glands, after which the virus may be transmitted by bite (Hardy et al. 1983). Under hot summer conditions, this process may be completed within 6–7 days, and the *Culex* vector mosquito is capable of transmitting virus during the next blood meal. In contrast, under cool conditions transmission may be delayed for more than 2 weeks or until the third or fourth blood meal. Therefore, the number of bites by the vector until transmission occurs is a convenient way to express the thermodynamics between the duration of the gonotrophic cycle and the extrinsic incubation periods. Some parasites may alter vector behavior and thereby increase the frequency of vector blood feeding and transmission. The plague bacillus, for example, remains within and eventually blocks the foregut of the flea vector, *Xenopsylla cheopis* (Kupferschmidt 1993). Regurgitation occurs during blood feeding and causes vector starvation, stimulating frequent blood-feeding attempts and more transmission at progressively more closely spaced intervals before the vector succumbs to starvation.

2.3.3 Transmission Cycles

Transmission cycles essentially describe the ecology or epidemiology of the parasites and vary considerably depending upon their complexity and the role of humans as hosts (Fig. 2.2). A vector-borne *anthroponosis* is a disease resulting from a parasite that can be transmitted among humans by one or more anthropophilic vectors.

Malaria, dengue, some forms of filariasis, and louse-borne typhus are examples of anthroponoses. Humans serve as reservoir hosts for these parasites, which may persist for years as chronic infections. Vectors of anthroponoses selectively blood feed upon humans and are intimately associated within domestic or peridomestic environments. Widespread transmission of an anthroponosis with an increase in the number of human disease cases during a specified period is an *epidemic*. When human cases reappear consistently over time and space, transmission is said to be *endemic*.

Zoonoses are diseases of animals caused by parasites that also may infect humans (Fig. 2.2). In most vector-borne zoonoses, humans and some domestic animals are not an essential component of the transmission cycle, but rather become infected when bitten by an infective vector that fed previously on an infectious animal host. Although humans frequently become ill, they

rarely circulate sufficient numbers of parasites to infect vectors and therefore are *dead-end hosts*. The *enzootic transmission cycle* (literally “in animals”) is the basic or primary animal cycle. When levels of enzootic transmission escalate, transmission may become *epizootic* (an outbreak of disease among animals). Transmission from the enzootic cycle to dead-end hosts such as humans is called *tangential transmission* (i.e., at a tangent from the basic cycle). Different or the same vector species may be responsible for enzootic, epizootic, and tangential transmission. *Bridge vectors* transmit parasites tangentially between enzootic and dead-end host species. Human involvement in zoonoses may depend on the establishment of a secondary *amplification cycle* among vertebrate hosts inhabiting the peridomestic environment.

Lyme disease, caused by infection with the spirochete *Borrelia burgdorferi*, is an example of a tick-borne zoonosis (Fig. 2.6) that is now

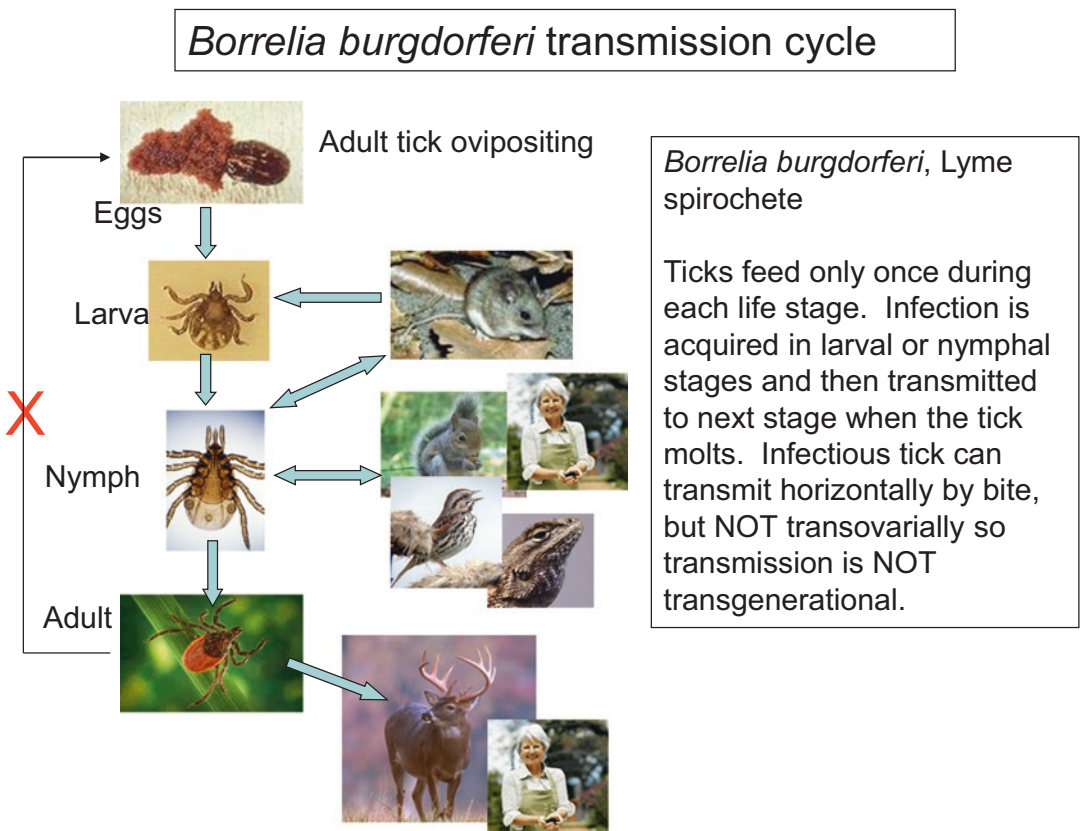


Fig. 2.6 Lyme disease spirochete, *Borrelia burgdorferi*, transmission cycle showing transstadial transmission

epidemic in eastern North America (Lane et al. 1991). If left untreated, the spirochete causes serious chronic disease in humans, presenting a variety of symptoms that may include arthritis and fatigue. The vectors are principally ticks in the *Ixodes ricinus* complex including *scapularis* in eastern and *pacificus* in western USA. Hard ticks require blood meals for both molting and reproduction. Larval ticks acquire *Borrelia* blood feeding on mice during summer that have infectious spirochetemias (number of spirochetes in the blood), maintain infections during winter, and then pass this infection transstadially to the nymphal stage the following spring. Nymphal ticks subsequently transmit their infection to a variety of hosts including rodents, squirrels, lizards, birds, and humans, but, if uninfected, also may acquire *Borrelia* during blood feeding. Lizards, some birds, and humans are refractory or “dead-end” hosts, and their infection may actually reduce the rate of *Borrelia* amplification. Infected nymphs also pass their infection transstadially to the adult stage, and adults may transmit to large mammals such as deer and perhaps humans during blood feeding, although deer seems to be refractory to infection. There is minimal evidence to support vertical transmission of *Borrelia* to the eggs, and therefore infected larval ticks and perhaps mice seem to be the reservoirs of infection. The changing landscape and reforestation of eastern USA, accompanied by large increases in whitetail deer and *Peromyscus* mouse populations, and the construction of housing adjacent to or within wooded areas have combined to create epidemiological situations conducive to large-scale outbreaks of Lyme disease. Infected immature tick populations residing in suburban gardens and lawns greatly increase the risk of transmission to humans.

2.4 Vector Incrimination

To understand the epidemiology and focus control on vector-borne disease, it is essential to establish which arthropod(s) is the primary vector(s) responsible for parasite transmission. Partial or incomplete vector incrimination has

resulted in the misdirection of control efforts at arthropod species that do not play a substantial role in either enzootic maintenance or epidemic transmission. Vector incrimination combines field and laboratory investigations that measure field infection rates, vector competence, and vectorial capacity.

2.4.1 Infection Rates

The collection of infected arthropods in nature is an important first step in identifying potential vectors, because it indicates that the candidate species feeds on vertebrate hosts carrying the infective parasite. Infection data may be expressed as *infection prevalence* (percentage of population infected at one point in time or number of vectors infected/number examined $\times 100$). The more commonly employed term, *infection rate*, usually refers to *infection incidence* and includes the number of new infections per unit of population over a specified time period. When the infection prevalence is low and arthropods are tested in groups or pools, data are expressed as a *minimum infection rate* (number of pools of vectors positive/total specimens tested/unit of time $\times 100$ or 1000). Minimum infection rates are relative values, with ranges delineated by pool size. For example, minimum infection rates of vectors tested in pools consisting of 50 individuals each must range from 0 to 20 per 1000 females tested. When pool sizes vary, a maximum likelihood estimate (MLE) of the infection rate should be used (Biggerstaff 2003).

It is important to distinguish between infected hosts harboring a parasite and infective hosts capable of transmission. In developmental and cyclodevelopmental vectors, the infective stages may be distinguished by location in the vector, morphology, or biochemical properties. Distinguishing infective from noninfective vectors is difficult, if not impossible, with viral or bacterial infections, because the parasite does not change form, although the location of recovery within the vector can be informative. The ability to transmit may be implied by testing selective body parts such as the legs, cephalothorax, salivary

glands, or head. With some tick pathogens, however, parasite movement to the mouthparts does not occur until after attachment. As mentioned previously, the transmission rate is the number of new infected hosts per time period. The annual parasite incidence frequently used in malaria control programs is the number of new human cases detected per 1000 population (or other units of population size) per year. The *entomological inoculation rate* is the number of potentially infective bites per host per unit of time. This frequently is determined from the human- or host-biting rate and the proportion of vectors that are infective and is calculated as bites per human per time period \times infectivity prevalence. In malaria, for example, this is the number of *Anopheles* positive for sporozoites biting humans per time period.

2.4.2 Vector Competence

The ability of an arthropod species to become infected with and transmit a parasite is *vector competence*. It typically is determined experimentally by feeding the candidate vector on a vertebrate host circulating the infective stage of the parasite, incubating the blood-fed arthropod under suitable temperature and at times humidity conditions, refeeding the arthropod on a noninfected susceptible vertebrate host, and then examining this host to determine if it became infected. This in some ways is similar to *Koch's postulates* used in microbiology. Because it often is difficult to maintain natural vertebrate hosts in the laboratory and control the concentration of parasites in their peripheral circulatory system, laboratory model hosts or more frequently artificial feeding systems are used to expose the vector to a known quantity of parasites and evaluate infection and transmission. *Susceptibility to infection* may be expressed as the percentage of arthropods that became infected among those blood feeding. When the arthropod is fed on a range of parasite concentrations, susceptibility may be expressed as the *median infectious dose* (ID_{50}) or the concentration of parasites required to infect 50% of the blood-fed arthropods. The

ability to transmit may be expressed either as the percentage of blood feeding or infected blood-feeding females that transmitted parasites or the percentage of recipient hosts that became infected when multiple arthropods were used per feeding.

Failure of a blood-fed arthropod to become infected with or transmit a parasite may be attributed to the presence of one or more barriers to infection (also see earlier vector immunity Sect. 2.2.3.4). For most parasites, the arthropod midgut provides the most important barrier (Hardy et al. 1983). Many viruses will grow in refractory or nonvector species, after they are inoculated into the hemocoel, thereby bypassing this *gut barrier*. *Arboviruses* (viruses transmitted by arthropods) must infect and replicate within the midgut epithelium and then escape through the basal lamina into the hemocoel, so it is possible to have *midgut infection* and/or *escape barriers*. After penetrating and escaping from the midgut, the parasite then must multiply and/or mature and be disseminated to the salivary glands or mouthparts. Arthropod cellular or humoral immunity may clear the infection at this point creating a *dissemination barrier*. Even after dissemination to the salivary glands, the parasite may not be able to infect or be transmitted from the salivary glands due to the presence of *salivary gland infection* or *escape barriers*, respectively. For parasites transmitted via the posterior station, vector competence may be expressed as the percentage of infected vectors passing infective stages of the parasite in their feces.

2.4.3 Vectorial Capacity

The formula for *vectorial capacity* summarizes quantitatively the epidemiological attributes of the vector relative to parasite transmission (Garrett-Jones 1970) within the Ross–MacDonald model (Macdonald 1957). Although originally developed for the *Anopheles* vectors of human malaria parasites and therefore most appropriate for anthroponoses, this model provides a framework to conceptualize how the components of transmission interact.

Vectorial capacity is expressed by the formula:

$$C = ma^2 (P^n) V / -\ln P$$

where C = vectorial capacity or new infections per infection per day, ma = bites per human per day, a = human-biting habit, P = probability of daily survival, n = extrinsic incubation period in days, and V = vector competence or innate transmission efficiency. This function comprises the entomological portion of the Ross–MacDonald model used to estimate the basic malaria reproductive rate, R_0 .

The *biting rate*, ma , frequently is estimated by collecting vectors as they attempt to blood feed and is expressed as bites per human per day or night (e.g., ten mosquitoes per human per night). The human-biting habit, a , combines vector-feeding frequency and host selection. *Feeding frequency* is the inverse of the duration of the gonotrophic cycle. Host selection patterns are determined by testing blood-fed vectors to determine what proportion feeds on humans or the primary reservoir. Therefore, if the blood-feeding frequency is 2 days and 50% of host-seeking vectors feed on humans, $a = (1/2 \text{ days}) \times (0.5) = 0.25$. In this example, $ma^2 = 10 \text{ bites/human/night} \times 0.25 = 2.5$. a is repeated, because infected vectors must refeed to transmit.

The probability of the vector surviving through the extrinsic incubation period of the parasite, P^n , requires information on the probability of daily survival, P , and the duration of the extrinsic incubation period, n . P is estimated either vertically by determining the age structure of the vector population or horizontally by marking cohorts and monitoring their death rate over time. In mosquitoes, P may be estimated vertically from the parity rate (proportion of parous females/number examined). In practice, $P = (\text{parity rate})^{1/g}$, where g is the length of the gonotrophic cycle. The duration of the extrinsic incubation period may be estimated from ambient temperature from data gathered during vector competence experiments by testing the time from infection to transmission for infected vectors incubated at different temperatures. Continuing

our example, if $P = 0.8$ (or 80% of the population survives per day) and $n = 10$ days, then the duration of infective life $P^n / -\ln P = 0.8^{10} / -\ln 0.8 = 0.48$ days. In addition it is useful to also account for vector competence, V . For this example, we will assume that 90% of vectors become infected and 90% of infected females are capable of transmission, so $V = 0.9 \times 0.9 = 0.81$. Therefore, vectorial capacity $C = 2.5 \times 0.48 \times 0.81$ or 0.97 parasite transmissions per infective host per day. When C approaches 1, the parasite can be maintained at a steady state. When $C > 1$, the parasite will increase and outbreaks may ensue, whereas when $C < 1$, the parasite may become focally extinct unless there are mechanisms in place for persistence without transmission or repeated introduction (see earlier section).

2.5 Interseasonal Maintenance

An important aspect of the ecology of vector-borne parasites is the mechanism(s) by which they persist between transmission seasons or outbreaks. Parasite transmission typically is most efficient when weather conditions are suitable for vector activity, reproduction, and population growth, and warm temperatures expedite parasite replication and dissemination within the vector and shorten the gonotrophic cycle increasing the frequency of host–vector contact. At temperate latitudes, winter temperatures frequently decrease to levels below which the parasite cannot replicate within the vector, vectors are driven into reproductive arrest, and vertebrate hosts may migrate or hibernate. Similar problems may face parasites at tropical latitudes, when transmission is interrupted by prolonged dry seasons. This seasonality which is characteristic of most vector-borne parasites may be due to either the periodic amplification of a constantly present parasite or to the consistent reintroduction of parasites following annual focal extinction.

There are several mechanisms that may allow parasite maintenance during unfavorable periods.

2.5.1 Continued Transmission

During periods of unfavorable weather, vectors may become active intermittently but continue to transmit parasites, although transmission rates may be slowed by cool temperature, low vector abundance, or infrequent blood feeding. At temperate latitudes with cool winters, the frequency of blood feeding and rate of parasite maturation in the vector are diminished. At tropical latitudes, widespread transmission may be terminated during extended dry seasons that reduce vector abundance and survival, even though blood-feeding activity may continue at refugia near permanent water sources. In both instances, transmission may be restricted spatially and involve only a small portion of the vertebrate host population. Therefore, human infections during adverse periods may be highly clumped, because vector and parasite dispersal is limited at this time.

2.5.2 Dormant Infected Vectors

Many vectors enter a state of dormancy as non-blood-feeding immatures or adults. Vertically infected vectors typically remain infected for life and therefore may maintain parasites during periods when horizontal transmission is interrupted. La Crosse encephalitis virus (Fig. 2.5), for example, is maintained during winter and drought periods within transovarially infected eggs of its vector, *Aedes triseriatus*. Infected eggs of this tree-hole mosquito may remain dormant and infected for several years and are able to withstand winter cold, summer heat, and extended dry periods. Here, the mosquito is the reservoir host. Inundation of eggs during the spring rains produces adult mosquitoes that are infected at emergence. In contrast, WNV may overwinter in vertically infected adult female *Culex* mosquitoes that have entered *diapause* (from the Greek *diapauēin* to “pause,” here insect hibernation). Termination of diapause, warming temperature, and the renewal of blood feeding initiate the transmission cycle among birds and host-seeking female *Culex*. Tick-borne parasites, such as Lyme

Borrelia, persist through winter within infected immature stages of the tick vector. Similarly, vectors that inhabit the nests of migratory hosts such as cliff swallows often remain alive and infected for extended periods until their hosts return.

2.5.3 Infected Vertebrate Hosts

Parasite maintenance may be accomplished by infected reservoir hosts that either continue to produce stages infective for vectors or harbor inactive stages of the parasite that relapse or recrudesce during the season when vectors are blood feeding. Adult filarial worms, for example, continue to produce microfilariae throughout their lifetime, regardless of the population dynamics or seasonality of the mosquito vector. In contrast, some Korean strains of *Plasmodium vivax* malaria overwinter as dormant stages in the liver of the human host and then relapse in spring concurrent with the termination of diapause by the *Anopheles* mosquito vector(s) (Brunetti et al. 1954).

2.5.4 Focal Extinction

Alternatively, parasites may become regionally extinct during unfavorable weather periods and then be reintroduced from refugia. Two possible mechanisms may allow the reintroduction of parasites:

Migratory vertebrate hosts. Many bird species overwinter in the tropics and return to temperate or subarctic breeding sites each spring, potentially bringing with them infections acquired at southern latitudes. However, finding evidence of infection to support this mechanism has been difficult (Reisen et al. 2010). It also is possible that the stress of long flights and ensuing reproduction triggers relapses of chronic infections. In addition, many large herbivores migrate annually between summer (or wet) and winter (or dry) pastures bringing with them an array of parasites as well as infestations of vectors such as ticks. Rapid

long-range human or commercial transportation is another possible mode for both vector and parasite introduction along frequently used routes (Tatem 2009).

Weather fronts. Infected vectors may be carried to long distances as “aerial plankton” by prevailing weather fronts (Sellers 1980). Consistent weather patterns such as the sweep of the southeastern monsoon from the Indian Ocean across the Indian subcontinent may passively transport infected vectors such as some *Anopheles* species hundreds of kilometers. Historically, the onset of western equine encephalitis virus activity in the north central USA and Canada has been attributed to the passive dispersal of infected mosquitoes by storm fronts as has the repeated introduction of Japanese encephalitis virus into northern Australia (Kay and Farrow 2000).

2.6 Surveillance

Tracking endemic and introduced vector-borne pathogens provides a challenge for health and surveillance (from French *surveiller*, “to watch over”) programs. Information on the number of cases over time and space in the human population can be gathered from morbidity and mortality records maintained by state or national governmental agencies. *Morbidity data* are records of illness that frequently are recognized clinically, whereas *mortality data* are records of the cause of death. These data vary greatly in their quality and timeliness, depending upon the disease, the accuracy of determining the cause of illness or death, and the rapidity of reporting. In the USA, the occurrence of confirmed cases of many vector-borne diseases including yellow fever, plague, malaria, and encephalitis by law must be reported to state health authorities. The frequency of case detection and accuracy of reporting systems are dependent on the type of surveillance employed and the ability of the medical or veterinary community to recognize suggestive symptoms and request appropriate confirmatory laboratory tests. In addition, some laboratory tests vary in their specificity and sensi-

tivity complicating the interpretation of laboratory results. Cases may be classified as suspect or *presumptive* based on the physician’s clinical diagnosis or results from nonspecific laboratory tests or *confirmed* based on a diagnostic rise in specific antibodies, the direct observation (or isolation) of the parasite from the case, or the results from an accepted assay such as demonstration of IgM in sera from presumptive WNV case. However, infections with many arthropod-borne parasites such as Lyme disease and WNV frequently are asymptomatic, present variable clinical symptoms, and therefore remain largely undiagnosed and underreported.

Surveillance for clinical cases may be active or passive. *Active surveillance* involves *case detection* by health workers who seek out and test suspect cases that fit a predetermined case definition. In malaria control programs, for example, a field worker may visit every household systematically and collect blood films from all persons with a current or recent fever. Fever patients are treated presumptively with antimalarial drugs, and these suspect cases then are confirmed by detection of malaria parasites in a blood smear or other samples. Confirmed cases are revisited; additional medication administered, if necessary; and a follow-up blood sample is taken. This active surveillance provides true population base infection rates. Frequently active surveillance is done by notification of hospitals to be aware of certain parasites thought to be actively present in the population.

Most surveillance programs rely on *passive case surveillance* and utilize clinical human or veterinary cases detected at medical or veterinary clinics. In this system individuals seeking medical attention at primary healthcare organizations are diagnosed by an attending healthcare professional who requests appropriate confirmatory laboratory tests. However, because many arthropod-borne diseases present a variety of nonspecific symptoms (e.g., headache, fever, general malaise, arthralgia), cases frequently may be missed or not specifically diagnosed. This *iceberg effect* (Fig. 2.7) is common among arthropod-borne viruses such as WNV, where ca. 80% of the infections are asymptomatic and ca.

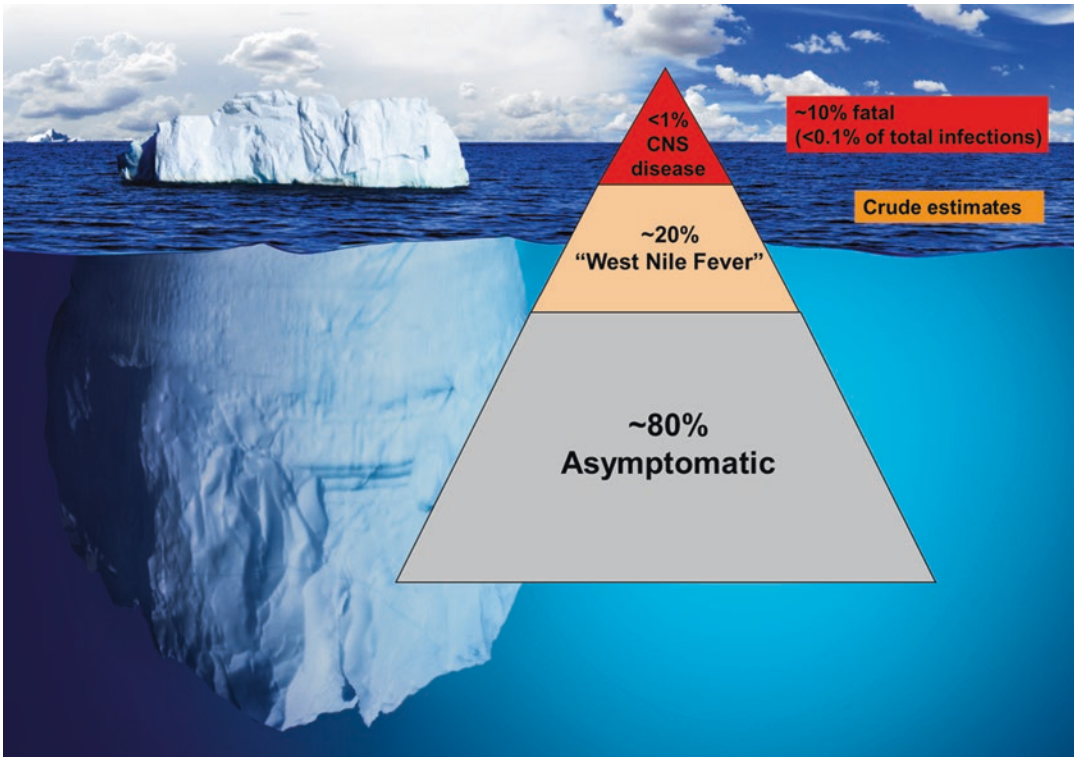


Fig. 2.7 Pyramid of West Nile virus disease, showing that only the “tip of the iceberg” of infections becomes clinical disease reported to surveillance programs (Iceberg

image from <https://littlemissholley.files.wordpress.com/2011/08/iceberg-logo.jpg>)

20% produce febrile disease of varying severity, only some of which are diagnosed; <1% of infections develop neuroinvasive disease with severe symptoms that are frequently diagnosed. As illustrated, most of the infections remain “below the surface” and go undetected. This problem is critical because often human data is the only surveillance information available for intervention decision support. Because many health decisions are driven by economics, underserved populations may appear to be devoid of infection/disease and therefore not receive preventive public health programs such as mosquito control.

The reporting system for clinical cases of vector-borne diseases must be evaluated carefully when interpreting surveillance data. This evaluation should account for the disease, its frequency of producing clinically recognizable symptoms, the official case definition, the sensitivity and specificity of confirmatory laboratory tests, and the type and extent of the reporting

system. Usually programs that focus on the surveillance of a specific disease and employ active case detection provide the most reliable epidemiological information. In contrast, broad-based community healthcare systems that rely on passive case detection typically produce the least reliable information, especially for relatively rare vector-borne diseases with nonspecific symptoms. Unfortunately, in the modern era, the extent of diagnosis and therefore the sensitivity of surveillance frequently are dependent upon the extent of medical insurance coverage and the physician’s decision to provide a definitive diagnosis.

In epidemiology, the *population* is the number of individuals at risk for infection in a given geographical area at a given time. *Incidence* is the number of new cases per unit of population per unit of time and is derived from two or more successive samples spaced over time (*longitudinal survey*). *Prevalence* is the frequency of both old

and new infections among members of a population. Prevalence typically is determined by a single point-in-time estimate (*cross-sectional survey*) and frequently is expressed as the percentage of the population tested that was infected or presented antibodies indicative of recent or previous infections. The level of parasite endemicity in a population may be graded as *hypoendemic* (low), *mesoendemic* (medium), or *hyperendemic* (high), depending upon the incidence and stability of infection and/or the immune status of the population. In malaria surveys, for example, the percentage of children with palpable spleens and the annual parasite incidence are used to characterize the level of endemicity. In endemic disease with continuous annual transmission, the percentage of individuals with sera positive for IgG antibodies typically increases as a linear function of age or residence history, whereas in hypoendemic disease with intermittent transmission, this function may be disjunct with specific age groups expressing elevated positivity rates. The occurrence of an above-normal number of human infections or cases is termed an *epidemic*. Health agencies, such as the World Health Organization (WHO), typically monitor incidence data to establish baseline criteria necessary to classify the level of endemicity and to decide when an epidemic is underway. A geographically widespread epidemic on a continental or global scale is called a *pandemic*.

Serological surveys (or *serosurveys*) are a useful epidemiological tool for determining the cumulative infection experience of a population with one or more parasites, host-related factors affecting the efficiency or risk of transmission, and reinfection rates. Antibodies are especially useful when the duration of infection with a parasite is brief, thereby limiting the chance of detecting infection. When coupled with morbidity data, serosurveys provide information on the ratio of apparent to inapparent infections. *Random sampling* representatively collects data from the entire population and may provide ecological information retrospectively by analysis of data collected concurrently with each serum sample. This information may assign risk factors for infection such as sex, occupation, and residence history or may help in ascertaining age-related

differences in susceptibility to disease. *Stratified sampling* targets a specific cohort, subpopulation, or geographical area. Although stratified samples may have greater sensitivity in detecting rare or contiguously distributed parasites, the data is not always readily extrapolative to infection or disease trends in the entire population. Repeated serological testing of the same individuals within a population can determine the time and place of infection by determining when individuals first become *seropositive*, i.e., serologically positive with circulating antibodies against a specific parasite. This change from seronegative to seropositive is called a *seroconversion* and frequently is used to detect infection in sentinel animals.

Forecasting human infection usually is accomplished by monitoring environmental factors, vector abundance, the level of transmission within enzootic and/or amplification cycles, and the numbers of human or domestic animal cases (Kramer 2012). As a general rule, the accuracy of forecasting is related inversely to the time and distance of the predictive parameter from the onset of human cases. Surveillance activities to validate or correct forecasts typically include the time series monitoring of environmental conditions, vector abundance, enzootic transmission rates, and clinical cases.

2.6.1 Environmental Conditions

Unusually wet or warm weather may indicate favorable conditions for vector activity or population increases and concurrently parasite transmission. Parameters frequently monitored include temperature, rainfall, snow pack (predictive of vernal flooding), and agricultural irrigation schedules. These are usually antecedent factors useful in the long-range prediction of risk. Remotely sensed data from satellite imagery is useful in showing changes in landscape vegetation.

2.6.2 Vector Abundance

Standardized vector monitoring at fixed sites and time intervals can be used to compare relative changes in temporal and spatial vector abun-

dance that validate environmental predictions and is useful in detecting an increased risk of parasite transmission. Trap type and placement are critical in effectively sampling vectors such as mosquitoes for surveillance purposes (Meyer and Reisen 2003). Devices are deployed in or adjacent to habitats that maximize their effectiveness in collecting the target mosquito species. Sampling in a systematic fashion over time can produce historical data useful in determining anomalous increases or decreases in abundance. Extraordinary increases in vector abundance and survival may accurately forecast increased enzootic transmission and, in turn, epidemics.

2.6.3 Enzootic Transmission Rates

For zoonoses, systematically monitoring the level of parasite infection in vector or vertebrate populations provides direct evidence that the parasite is present and being actively transmitted. The level of enzootic transmission usually is directly predictive of the risk to humans or domestic animals. Enzootic transmission activity may be monitored by measuring vector infection rates, vertebrate host infection rates, sentinel seroconversion rates, and the number of clinical cases.

2.6.3.1 Vector Infection Rates

Sampling vectors and testing them for parasites determine the level of infection in the vector population. When vectors are tested individually, prevalence data are expressed as percentages; e.g., ten females infected per 50 tested are a 20% infection rate. When combined with abundance estimates, infection rates also may be expressed as the *entomological inoculation rate* or the number of infectious vectors per sampling unit per time interval; e.g., 100 bites per human per night $\times 0.2$ infectious rate = 20 infective bites per human per night. When infection rates are low, vector populations large, and sampling independent of vector age, vectors usually are tested in lots or *pools*. It is statistically advantageous to keep pool size constant and therefore

the chance of detecting infection the same. Because there may be >1 infected vector per pool, infection rates are expressed as a minimum infection rate = positive pools/total individuals tested $\times 100$ or 1000. There are several new mathematical approaches to calculating these estimates that rely on maximum likelihood estimation methods.

2.6.3.2 Vertebrate Host Infection Rates

Introduced zoonoses, such as sylvatic plague in North American rodents, WNV in American crows, or yellow fever virus in South American monkeys, frequently produce mortality that may be used to track epizootics of these parasites over time and space. Large numbers of dead American crows have been a hallmark of the ongoing WNV epidemic in North America, and counts of reports by the public have been used for surveillance purposes to indicate recent transmission as well as to forecast human risk using predictive spatial models (Carney et al. 2011). In contrast, endemic zoonoses rarely result in vertebrate host mortality. Collecting and testing reservoir or amplifying hosts for infection is necessary to monitor the level of enzootic parasite transmission. Stratified sampling for these parasites (directly by parasite isolation or indirectly by seroprevalence) usually focuses on the young of the year to determine ongoing or recent transmission.

Monitoring the incidence of newly infected individuals in a population over time is necessary to detect increased transmission activity. Because many parasites are difficult to detect or are only present for a limited time period, sampling frequently emphasizes the monitoring of seropositivity or seroprevalence. Testing for IgM antibody, which rises rapidly after infection, is parasite specific, and decays relatively quickly can indicate the level of recent infection, whereas monitoring IgG antibody documents the population's historical experience with the parasite. Sampling, marking, releasing, recapturing, and resampling wild animals are most useful in providing information on the time and place of infection in free-roaming animal populations.

2.6.3.3 Sentinel Seroconversion Rates

Sentinels typically are animals that can be monitored over time to quantify the prevalence of enzootic parasite transmission. Trapping wild animals or birds is labor intensive, and determining seroprevalence may provide little information on the time and place of infection, especially if the host is a bird species that has a large home range. To circumvent this problem, caged or tethered natural hosts or suitable domestic animals of known infection history are placed in sensitive habitat and repeatedly bled to detect infection. A suitable sentinel should be fed upon frequently by the primary vector species, be easy to diagnose when infected, be unable to infect additional vectors (i.e., not serve as an amplifying host), not succumb to infection, and be inexpensive to maintain and easy to bleed or otherwise sample for infection. In the USA, flocks of seronegative chickens are placed at farmhouses or other suitable localities, housed in standard coops, and then bled weekly or biweekly to determine seroconversions to viruses such as WNV that have a natural mosquito–bird transmission cycle. Small blood samples taken on filter paper can be tested by a semiautomated enzyme-linked immunosorbent assay (ELISA) to detect seroconversions. Because the chickens are confined and the date of seroconversion known, the time and place of infection are determined, while the number seroconverting estimates the intensity of transmission.

2.6.4 Clinical Cases

Detecting infection among domestic animals may be an important indication that an epizootic is underway and that the risk of human infection has become elevated. Domestic animals such as horses and pigs often are more exposed to vectors than humans and therefore provide a more sensitive indication of parasite transmission, unless they are protected by widespread vaccination campaigns. Clinical human cases in rural areas in close association with primary transmission cycles may be predictive of future epidemic transmission in urban settings.

2.6.4.1 Intervention

Vector-borne diseases frequently affect only a small percentage of the human population or do not impart long-lasting protective immunity (e.g., malaria), thereby making vector control the intervention of choice. Integrated vector control programs attempt to maintain vector abundance below thresholds necessary for the transmission of parasites to humans or domestic animals. When these programs fail, personal protection by repellents or insecticide-impregnated clothing, bed nets, or curtains is often the only recourse. Vaccination may be a viable alternative method of control for specific vector-borne diseases, if the vaccine imparts lasting immunity as in the case of yellow fever or Japanese encephalitis viruses. However, many parasites such as malaria have evolved to the point where infection elicits a weak immune response that provides only short-term and marginal protection without continued reinfection. The need for continued revaccination at short intervals severely limits their global usefulness, especially in developing countries where delivery systems are rudimentary. Although breakthroughs in chemotherapy have been useful in case management, it still remains the mandate of the medical/veterinary entomologist to devise strategies which combine epidemiological and ecological information to devise ways to effectively reduce or eliminate the risk of disease.

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