Epidemiology

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1 INTRODUCTION

The word *rabies* may invoke profound indifference, keen attention, or powerful fear among the public, physicians and related human health care providers, public health professionals, veterinarians, pet owners, and caregivers of domestic and wild animals. Looking at the last 50 years of rabies transmission patterns, challenges are clear. In North America, an extensive but economically pressured public health infrastructure continues to provide protection from an overwhelmingly and universally lethal disease for which there is limited and, with recent economic developments, diminishing support for diagnosis, surveillance, and public and professional education essential for disease prevention.

Rabies has the highest mortality of any known infectious agent with only 3 survivors (one was pre-exposure vaccinated) among the 100 human rabies cases in the USA from 1960–2007. In comparison, the second most lethal viral disease, Ebola hemorrhagic fever, resulted in the death of 18 of 26 cases during a 2000 outbreak in Masindi, Uganda (Borchert et al., 2011). The global burden of rabies is still from sustained transmission of canine-adapted rabies virus variants among domestic dog populations, mainly in Asia and Africa (Lembo et al., 2011). The large-scale threat of rabies exposure to humans and domestic animals in Europe and North America was significantly reduced a number of decades ago through coordinated, methodical, population-based vaccination of dogs and control of stray dog populations. Similar to trends in the

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USA and Europe during the 1950s and 1960s, recent substantial improvements in canine rabies control have occurred in Latin America, reducing the incidence of human disease (Schneider et al., 2011; Ruiz & Chavez, 2010; Belotto, 2004). In practicality, these techniques could be applied globally to push remaining canine rabies virus variants to extinction, if sufficient effort and resources were applied in a cooperative and coordinated manner towards this goal.

Due to elimination of dog-to-dog transmission, trends in animal and human rabies in many areas of the world changed substantially during the last half of the 20th century. In developed countries, human rabies was decreased due to fewer exposures from canine rabies virus variants and the availability of better prophylactic biologics but, in many areas, an increase in rabies transmission among wildlife was recognized. In the USA, the increase in reported wildlife rabies between 1970 and 1990 was due to intensive and geographically extensive epizootics among skunk and raccoon populations. However, enhanced surveillance among other wildlife reservoir species—bats, for example—also influenced the number of reports submitted from states for annual summary.

Overall animal rabies trends as determined by legally mandated, but passive, surveillance efforts in North America indicate a decline from over 20,000 cases per year in the late 1980s to the current level of approximately 6,000–8,000 per year, with the vast majority of cases occurring in the USA (Figure 3.1). These trends reflect the recent success in canine
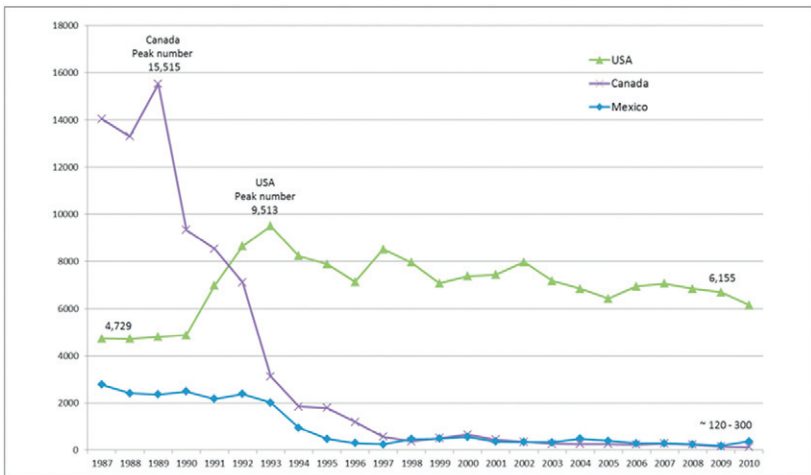

FIGURE 3.1   **Total number of rabies cases diagnosed in North America (Canada, USA, Mexico), 1987–2010.**[1]

[1]Note that the 2009 case total from Mexico is provisional, and the 2010 value is an estimate based on 4 times the first quarter number (n = 92 to date).

rabies control in Mexico, as well as a decline in red fox rabies in Canada due to oral vaccination. The continuing enzootic of raccoon rabies in the USA and its incursions into Canada still pose significant challenges to human and veterinary health (Boyer, Canac-Marquis, Guerin, Mainguy, & Pelletier, 2011; Fehlner-Gardiner et al., 2012; Rosatte et al., 2009).

Despite the historic extinction of canine rabies virus variants in most of North America, numerous rabies virus variants are found among various terrestrial wildlife species (Figure 3.2), and, when considered with the growing number of variants identified among a variety of insectivorous bat species across the Americas and hematophagous bats in Latin America, these constitute an ever-present risk of potential exposure. Sometimes animal owners and the public in the USA are surprised to discover that between 6,000 and 8,000 animal rabies cases are diagnosed every year (Figure 3.3). These cases represent a subset of all naturally occurring cases

FIGURE 3.2 **Geographic occurrence of terrestrial wildlife rabies virus variants in North America.** The distribution of terrestrial rabies virus variants in North America is delineated by the primary host species or the common name of the group of terrestrial carnivore species serving as reservoir hosts. Numerous rabies virus variants in a number of insectivorous bat species occur throughout the main part of the continent from Alaska and south throughout Mexico and South America. *Data adapted from Velasco-Villa (2006) and USA annual rabies surveillance reports.*
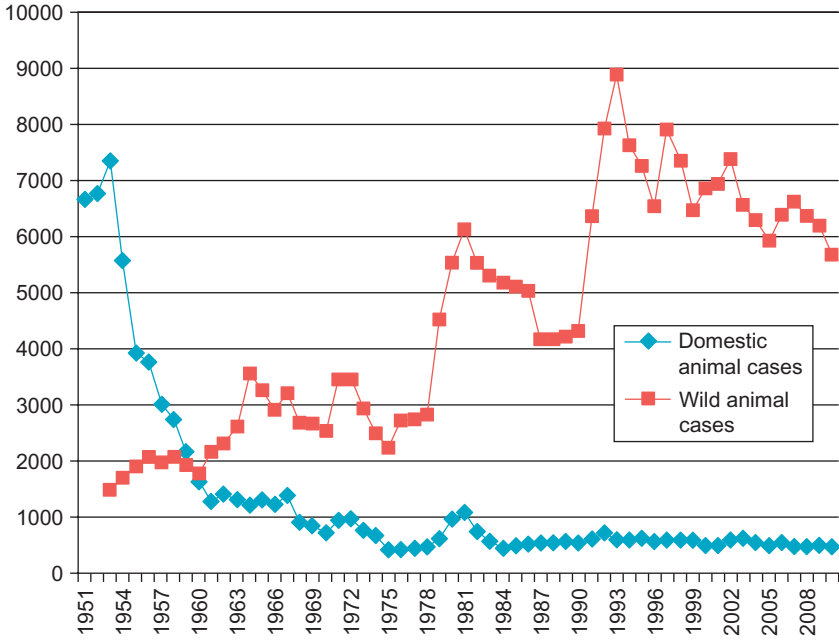
FIGURE 3.3 **Cases of rabies in domestic and wild animals in the USA, 1951–2010.**
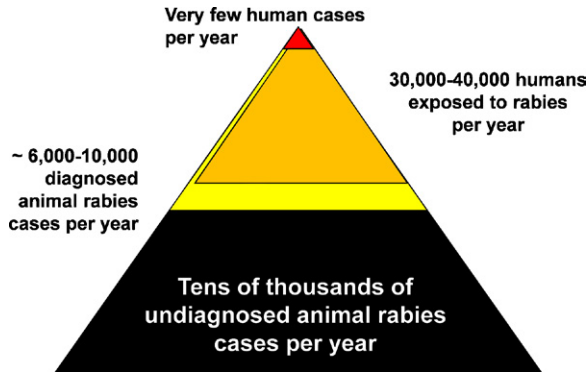
FIGURE 3.4 **Measurable impacts of enzootic and epizootic rabies and the "tip-of-the-iceberg" concept.**

(Figure 3.4). Moreover, humans travel, domestic, and in some instances wild animals, are moved, and bats, implicated as reservoirs for a variety of rabies virus variants, fly. The risk of exposure to rabies is global. However, understanding global and local transmission patterns and the pathogenesis of the disease will facilitate responsible management of potentially exposed persons and animals towards disease prevention.

2 GLOBAL EPIDEMIOLOGY

The disease rabies is defined as an acute fatal encephalomyelitis in mammals, resulting from infection by any of the viruses in the genus Lyssavirus. As of 2012, the number of recognized species within the genus *Lyssavirus* has grown from seven in 2002 (Childs, Krebs, & Smith, 2002) to 12 (Table 3.1). Since 2003, five novel lyssaviruses were accepted as new species by the International Committee on Taxonomy of Viruses (ICTV) including four unique isolates originating from Eurasia, each from different species of insectivorous bats (Hanlon et al., 2005) and another unique isolate, Shimoni bat virus (SHIBV), from Africa (Kuzmin et al., 2010).

The type species, rabies virus (RABV), is distributed worldwide among mammalian reservoirs consisting of carnivores and bats. RABV, often referred to as genotype 1 (GT 1) and historically as serotype 1 (ST 1), is comprised of a number of related viruses capable of initiating acute fatal neurological disease among mammals. This group is responsible for the majority of human and animal deaths both over the centuries and at present. The term 'genotype' has been applied to lyssaviruses since molecular techniques replaced serotyping as a method of classification (Bourhy, Kissi, & Tordo, 1993). However, the ICTV recognizes viral species rather than genotypes.

Lagos bat virus (LBV), referred to as genotype 2 (GT 2) is found in pteropid bats in sub-Saharan Africa with infrequent spillovers into other species (Markotter et al., 2008). The reservoir host for Mokola virus (MOKV)(genotype 3 (GT 3)) remains elusive but isolates exist from shrews, cats, dogs, a rodent, and two humans in sub-Saharan Africa (Sabeta et al., 2007; Nel et al., 2000). Duvenhage virus (DUVV)(genotype 4 (GT 4)) has been isolated from insectivorous bats and humans who died after bat bites, again, in sub-Saharan Africa (Markotter et al., 2008; van Thiel et al., 2009). The primary host species of European bat lyssavirus, type 1 (EBLV1)(genotype 5 (GT 5)) is the Serotine bat (*Eptesicus serotinus*) and occurs in insectivorous bats across Europe, with occasional infection of humans (Fooks et al., 2003; Kuzmin, Hughes, & Rupprecht, 2006). European bat lyssaviruses, type 2 (EBLV2)(genotype 6 (GT 6)) are isolated primarily from insectivorous bats in the *Myotis* genus and from infected humans following a bite from bats in northwestern Europe (Fooks et al., 2003). The death of a Scottish bat conservationist due to EBL2 infection was the first indigenously acquired case of rabies in the UK in 100 years (Nathwani et al., 2003).

Australian bat lyssavirus (ABLV)(genotype 7 (GT 7)) was first described in 1996 (Speare et al., 1997), is diagnosed with standard rabies diagnostic reagents, prevented with traditional rabies vaccines, and results in fatal human disease that is indistinguishable from classic rabies

TABLE 3.1 Recognized or Proposed Members of the Genus *Lyssavirus*, Family *Rhabdoviridae*

Virus Species Name ICTV Abbreviation[a]	Species Implicated in Maintenance	Distribution	Annual Human Deaths	Reference
Rabies (ST 1/GT 1) RABV	Dogs, wild carnivores, bats	Worldwide (with exception of Australia, Antarctica, and designated rabies-free countries)	>55,000	(Shope, 1982)
Lagos bat (ST 2/GT 2) LBV	Bats-Megachiroptera; *Eidolon helvum*, *Micropterus pusillus, Epomophourus wahlbergi*	Africa: Central African Republic, Ethiopia, Nigeria, Senegal, South Africa	not reported	(Bougler and Porterfield, 1958)
Mokola (ST 3/GT 3) MOKV	Uncertain. Shrew-Insectivora; *Crocidura* spp.; Rodentia; *Lopyhromys sikapusi*	Africa: Cameroon, Central African Republic, Ethiopia, Nigeria, South Africa, Zimbabwe	occasional	(Shope et al., 1970)
Duvenhage (ST 4/G 4) DUVV	Bats-Microchiroptera; *Miniopterus schreibersii, Nycteris gambiensis, N. thebaica*	Africa: South Africa, Guinea, Zimbabwe	occasional	(Meredith et al., 1971)
European bat Lyssavirus 1 (GT 5) EBLV-1	Bats-Microchiroptera; *Myotis dasycneme, M. daubentonii*	Europe	occasional	(Bourhy et al., 1993)
European bat Lyssavirus 2 (GT 6) EBLV-2	Bats-Microchiroptera; *Eptesicus serotinus*	Europe	occasional	(Bourhy et al., 1993)

Australian bat Lyssavirus (GT 7) ABLV	Bats-Megachiroptera; *Pteropus alecto, P. scapulatus*	Australia, 1996; possibly SE Asia mainland	occasional	(Speare et al., 1997)
Aravan virus ARAV	Bat (single isolate) Microchiroptera; *Myotis blythi*	Kyrgyzstan, 1991	not reported	(Arai et al., 2003)
Khujand virus KHUV	Bat (single isolate) Microchiroptera; *Myotis mystacinus*	Tajikistan, 2001	not reported	(Kuzmin et al., 2003)
Irkut virus IRKV	Bat (single isolate) Microchiroptera; *Murina leucogaster*	Eastern Siberia, 2002	not reported	(Kuzmin et al., 2003)
West Caucasian bat virus WCBV	Bat (single isolate) Microchiroptera; *Miniopterus schreibersi*	Caucasus Mountains, 2003	not reported	(Botvinkin, 2003)
Shimoni bat virus SHIV	Bat (single isolate), Leaf-nosed (*Hipposideros commersoni*)	Kenya	not reported	(Kuzmin et al., 2010)
Bokeloh virus[b] BOKV	Bat (single isolate) Natterer's bat (*Myotis nattererii*)	Germany	not reported	(Freuling et al., 2011)
Ikoma virus[b] IKOV	African civet (single isolate) (*Civettictis civetta*)	Tanzania	not reported	Marsten et al., 2012)

[a]*ICTV = International Committee on Taxonomy of Viruses, 2011 updates.*
[b]*As yet unclassified new lyssavirus*

(Hanna et al., 2000; Samaratunga, Searle, & Hudson, 1998; Warrilow, 2005; Warrilow, Smith, Harrower, & Smith, 2002). In regard to international travel of domestic animals, Australia is considered "rabies-free" by the World Health Organization, despite these rabies diagnostic and fatal clinical observations and prevention practices with rabies biologics. The Australian bat lyssaviruses circulate among insectivorous and pteropid bats. As previously mentioned, five new species were accepted as new genus lyssavirus members in the 8th report update of the ICTV including Aravan virus (ARAV) and Khujand virus (KHUV) which were each isolated from an insectivorous bat of the *Myotis* genus in Central Asia (Kuzmin et al., 2003), Irkut virus (IRKV) which was isolated from an insectivorous bat, *Murina leucogaster* in eastern Siberia (Kuzmin, Hughes, Botvinkin, Orciari, & Rupprecht, 2005), West Caucasian bat virus (WCBV) which was isolated from an insectivorous bat, *Miniopterus schreibersi* in southeastern Europe (Botvinkin et al., 2003) and Shimoni bat virus identified from an adult female Commerson's leaf-nosed bat (*Hipposideros commersoni*). The latter virus was identified from a dead bat during active disease surveillance in a cave near the southern coast of Kenya (Kuzmin et al., 2010). New lyssaviruses continue to be discovered and present new challenges but the breadth of their occurrence, and the impact of these rabies-related viruses in regard to human and animal mortality appear to be substantially less than those from the type species, RABV.

More recently, Bokeloh bat lyssavirus (BBLV) isolated from a Natterer's bat (*Myotis nattererii*) in Germany (Freuling et al., 2011) and Ikoma virus (IKOV) ioslated from an African civet (*Civettictis civetta*) in Tanzania (Marston et al., 2012) have been proposed as novel members within the genus, although they are not yet formally recognized.

Rabies virus variants can be differentiated by their antigenic characteristics, as measured by differential binding patterns with monoclonal antibodies (Rupprecht, Glickman, Spencer, & Wiktor, 1987; Smith, 1988), and by variations in nucleotide substitutions in their single stranded negative-sense RNA genome (Nadin-Davis, Casey, & Wandeler, 1994; Sacramento, Bourhy, & Tordo, 1991; Smith, Orciari, Yager, Seidel, & Warner, 1992). Based on these tools, it is evident that rabies virus is maintained in diverse mammalian species within the Orders Carnivora and Chiroptera. Humans do not contribute to the maintenance of rabies virus or other lyssaviruses and are considered "dead-end" hosts. Scant evidence exists for natural human-to-human transmission (Fekadu et al., 1996).

Rabies disproportionately affects populations of the species serving as the reservoir host for a specific variant. Transmission of rabies virus is primarily among conspecifics, with cross-species transmission to other mammals usually depending upon direct interactions with infected

individuals of the reservoir host species (Blanton, Palmer, Dyer, & Rupprecht, 2011; Blanton, Palmer, & Rupprecht, 2010; McQuiston, Yager, Smith, & Rupprecht, 2001).

Conceptually, rabies virus resembles a metapopulation in which genotypically and phenotypically distinguishable rabies virus variants are adapted to, and maintained by, a single or a few mammalian species, which, *in toto*, constitute the GT 1/ST 1 of genus *Lyssavirus*. The classic definition of a metapopulation is a population of subpopulations that are linked by occasional movements (Barbour & Pugliese, 2004). In the case of rabies virus, movements are represented by the occasional cross-species transmission (i.e., spillover) of rabies virus variants from a reservoir host to a secondary species in which the original variant subsequently becomes adapted to sustained transmission within the secondary species, coincident with the genetic and phenotypic changes indicative of its emergence as a novel and unique sub-variant of rabies.

The epidemiology of human and animal rabies almost invariably reflects the regional terrestrial virus variants maintained within their specific animal reservoirs, and the opportunity for other animal species and human-animal interactions (Anderson, Nicholson, Tauxe, & Winkler, 1984; Feder, Jr., Petersen, Robertson, & Rupprecht, 2012; McQuiston et al., 2001; Noah et al., 1998). Exceptions to this are the occasional spillover of bat-associated rabies virus variants to domestic animals and humans (McQuiston et al., 2001; Messenger, Smith, & Rupprecht, 2002), which are more difficult to spatially map with accuracy due to the ecology of the bat species involved. In addition, "imported" cases of rabies occur following travel or translocation of a human or animal that succumbs to rabies in the new location due to a virus variant from a country of origin.

Animals are also subject to intentional or accidental long distance movement by humans. Translocation of raccoons was responsible for one of the most intense wildlife rabies epizootics on record, the mid-atlantic raccoon rabies epizootic (Nettles, Shaddock, Sikes, & Reyes, 1979). Another very dangerous translocation was responsible for cases of coyote/dog variant rabies among coyotes in Florida, where the virus was introduced with translocated coyotes from Texas (Anonymous, 1995).

Events of viral evolution and adaptation are generally inferred by molecular epidemiologic reconstruction (Hayman et al., 2011; Hughes, Orciari, & Rupprecht, 2005; Kuzmin et al., 2012; Nel et al., 2005; Smith, Lucey, Waller, Childs, & Real, 2002; Talbi et al., 2010). By molecular phylogenetic analyses, a bat ancestry is hypothesized as the origin of rabies virus variants affecting terrestrial carnivores (Badrane & Tordo, 2001). In North America, a molecular clock model suggests the date of divergence of extant bat-associated rabies from the most recent common ancestor occurred about 1651–1660 (Hughes et al., 2005). The bat rabies virus variants found in Latin America among the common vampire bat (*Desmodus*

rotundus) and species of the genus *Tadarida*, family *Mollosidae* or free-tailed bats, are closest to the earliest common ancestor. Adaptation of rabies virus variants to species of bats living in medium sized colonies, genera *Eptesicus* and *Myotis*, occurred more rapidly and earlier in time than did adaptation to the more solitary genera, *Lasionycteris, Pipistrellus*, and *Lasiuris* (Hughes et al., 2005). In certain instances, as with red foxes on Prince Edward Island (Daoust, Wandeler, & Casey, 1996) and striped skunks in Arizona (Leslie et al., 2006), sustained transmission of bat variants of rabies virus within terrestrial carnivore populations has occurred. Significantly, the identification of specific virus metapopulations within readily identifiable mammalian host species has served as a basis for primary prevention through education of the public and pet owners in regard to risk and prevention, appropriate management of domestic animals at-risk for exposure, and assessment and management of exposed persons. Moreover, this understanding is crucial for experimental approaches towards species-specific design of control measures, such as delivering rabies vaccines by parenteral or oral routes for immunizing sylvatic reservoir hosts and domestic dogs (Charlton et al., 1992; Cliquet et al., 2012; Frontini et al., 1992; Gruzdev, 2008; Hanlon et al., 1989; MacInnes, Tinline, Voigt, Broekhoven, & Rosatte, 1988; Potzsch, Kliemt, Kloss, Schroder, & Muller, 2006; Rupprecht, Hanlon, & Slate, 2004; Wandeler, Capt, Kappeler, & Hauser, 1988) (also see Chapter 13).

3 ROUTES OF RABIES VIRUS TRANSMISSION

3.1 Natural Routes of Transmission

The most common and natural route of rabies virus exposure and transmission is through an animal bite (World Health Organization, 2005; Manning et al., 2008). Contamination of fresh, open bleeding wounds with infectious material is another means of exposure to rabies virus, particularly, for example, if the wounds have been inflicted by the rabid animal through saliva-contaminated claws. Contamination of intact skin with saliva is not considered an exposure to rabies (Manning et al., 2008). Contamination of mucous membranes is a much less effective route of potential exposure to rabies than through bites or open wounds. When exposure occurs by the oral route, rabies occurs infrequently and in some cases, vaccination occurs (Baer, Abelseth, & Debbie, 1971; Baer, Broderson, & Yager, 1975). Certainly ocular exposure through transplantation of corneas from humans dying of rabies generally results in rabies in the recipient (Houff et al., 1979; Javadi, Fayaz, Mirdehghan, & Ainollahi, 1996; Maier et al., 2010; Vetter et al., 2011). However, the risk of transmission through direct contamination of an intact corneal surface is unknown,

and no naturally occurring cases have implicated this route. Rabies virus infection possibly acquired by droplets or aerosolized virus has been described in two persons visiting Frio Cave in Texas (Irons, Eads, Grimes, & Conklin, 1957). Millions of Mexican free-tailed bats (*Tadarida brasiliensis*) congregate in this cave, and rabies virus is endemic within the bat population (Humphrey, Kemp, & Wood, 1960). Experimental studies with animals and with an electrostatic precipitation device suggest that air-borne transmission of rabies virus can occur under these exceptional circumstances (Constantine, 1962; Winkler, 1968). It is clear that intranasal exposure to droplets or spray is a potentially dangerous route of exposure because of direct olfactory pathway spread to the brain (Winkler, Fashinell, Leffingwell, Howard, & Conomy, 1973; Anonymous, 1977; Johnson, Phillpotts, & Fooks, 2006), but rabies virus rarely forms a natural aerosol, relegating the inhalation or intranasal route to one of minor importance in the natural history of transmission and disease.

The most important route of rabies virus transmission to humans is animal bite (Manning et al., 2008). Rare reports exist of human rabies following transmission by licks to mucous membranes (Leach & Johnson, 1940), transdermal scratches contaminated with infectious material, and even improperly inactivated rabies vaccines (Para, 1965). Two cases of possible human-to-human transmission of rabies have been described from Ethiopia, although it is not clear if other potential sources of exposure were unlikely (Fekadu et al., 1996). Although transplacental transmission of rabies virus has been reported in a single human case (Sipahioglu & Alpaut, 1985), infants have survived delivery from mothers infected with rabies, when the child received post-exposure prophylaxis (PEP) (Lumbiganon & Wasi, 1990).

There is little documentation for natural rabies transmission by simple contact with virus-infected tissue, although isolated reports suggest infection following butchering of infected carcasses, (Anonymous, 2004; Tariq, Shafi, Jamal, & Ahmad, 1991; Noah et al., 1998) and recently an unvaccinated veterinarian using no personal protective equipment (i.e., gloves, eye protection, etc.) prepared a domestic herbivore for submission for rabies testing and later succumbed to rabies (Brito et al., 2011). In the United States, ingestion of unpasteurized milk from rabid cows has been considered a possible exposure to virus (Centers for Disease Control and Prevention, 1999). Scratches received from a rabid animal could potentially be contaminated with saliva containing rabies virus, and in the United States PEP is considered for persons in these situations (Manning et al., 2008).

Many of the recent human rabies cases in the United States have no documented history of animal bite reported by the patient, relatives, or close companions (Feder, Jr. et al., 2012; Noah et al., 1998). The most likely reason is ignorance regarding the potential rabies exposure risk from a bat encounter and the very minor wound from a bite from a small

FIGURE 3.5   **Rabies-positive red bat (*Lasuirus borealis*).**

FIGURE 3.6   **Tricolored bat (*Perimyotis subflavus*) and silver-haired bat (*Lasionycterus novtivagans*).**

bat which, unlike bites from carnivores, would not prompt a medical consult solely on the basis of trauma (Figures 3.5 and 3.6).

3.2 Iatrogenic Routes of Transmission

Although rare, iatrogenic human-to-human transmission of rabies has been well documented for recipients of transplanted human tissues. For example, rabies was not recognized in one donor and resulted in deaths among four recipients of kidneys, a liver, and an arterial segment from the index patient in 2004 in the United States (Anonymous, 2004; Noah et al., 1998; Srinivasan et al., 2005). Subsequently, in 2005, three rabies deaths occurred among recipients of organ transplants in Germany (Noah et al., 1998; Maier et al., 2010).

4 RISK AND PREVENTION OF RABIES FOLLOWING AN EXPOSURE

The risk of developing rabies depends on the anatomical site and severity of the bite, the species inflicting the wound, and presumably the rabies virus variant. Published data indicate the risk of developing clinical rabies in unvaccinated persons was 50–80% following multiple, severe head bites; 15–40% following multiple, severe finger, hand, or arm bites; and 3–10% following multiple, severe leg bites inflicted by large terrestrial carnivores, such as wolves or bears (Hattwick et al., 1974). In general, exposure to most body fluids or blood from a rabid animal or a rabid human, with the notable exception of saliva and tears (Anderson et al., 1984; Helmick, Tauxe, & Vernon, 1987), is not regarded as an exposure to rabies (Manning et al., 2008). However, in certain circumstances, laboratory technicians reporting a definite and significant exposure (e.g., a technician cut by a broken specimen container from a rabid patient) to CSF or urine from a human rabies case have been given PEP (Anderson, Williams, Jr., Layde, Dixon, & Winkler, 1984).

In general, modern cell culture derived vaccines, when properly administered with anti-rabies immunoglobulin (RIG), are virtually 100% effective in preventing rabies after an exposure has occurred (Manning et al., 2008). The need for administration of both vaccine and RIG for the prevention of rabies following exposure has been appreciated for more than a half-century (Baltazard & Bahmanyar, 1955; Hemachudha et al., 1999). Vaccine failures have been reported when RIG was not infiltrated around the bite site (Anonymous, 1987; Wilde et al., 1996) or when RIG was omitted in treatment (Gacouin et al., 1999). Potential vaccine failures and failure to adequately seroconvert to nerve tissue origin and cell culture derived vaccines among persons concurrently taking chloriquine for malaria have been documented (Pappaioanou et al., 1986). There are no contraindications for rabies PEP; if one is exposed to rabies, PEP is warranted irrespective of pregnancy, infancy, old-age, or concurrent infections (Manning et al., 2008).

4.1 WHO and the Advisory Committee on Immunization Practices (ACIP) Recommendations for Pre- and Post-exposure Prophylaxis (PEP)

In the United States, all potential rabies virus exposures are treated with HRIG infiltration around the site of exposure and intramuscular vaccination with either the full five doses (Manning et al., 2008) or just the first four (Rupprecht et al., 2009). Two vaccines, Imovax and RabAvert, are licensed in the United States for PEP or pre-exposure

immunization (Manning et al., 2008). The WHO recommends PEP prophylaxis according to categorical grades of potential rabies virus contact and exposure and lists a number of suitable vaccines for human and animal use (World Health Organization, 2005). Grade II exposures (potential contact with rabies virus through nibbling of uncovered skin or minor scratches or abrasions with bleeding) require vaccination, unless or until the animal is determined to be negative for rabies virus infection. Grade III exposures are potential contact with rabies virus by single or multiple transdermal bites or scratches, licks, or broken skin, or contamination of mucous membrane with saliva (i.e., licks), or exposure to bats and requires vaccination and RIG (World Health Organization, 2005). An additional difference from ACIP recommendations in the United States is that WHO recommends the use of intradermal vaccination for PEP and pre-exposure vaccination with two commercially available vaccines, which permits significant cost savings (World Health Organization, 2005).

As many as 40,000 persons annually may receive PEP in the United States (Krebs, Long-Marin, & Childs, 1998), although frequently prophylaxis may be administered in situations where it is not indicated (Noah et al., 1996). Increasingly, mass human exposures to rabid animals have depleted the local availability of rabies biologicals in the United States and resulted in expensive episodes (Robbins, Eidson, Keegan, Sackett, & Laniewicz, 2005; Rotz, Hensley, Rupprecht, & Childs, 1998). Somewhat to the surprise of public health officials, it appears that when recommendations for PEP are not adhered to in an emergency room setting in the United States, more often PEP is withheld when it should be recommended (Moran et al., 2000). Although closer adherence to recommended policies would be ideal, it is unclear whether this would increase or decrease rabies biological use in the United States.

4.2　PEP for Non-rabies Lyssaviruses

Rabies vaccines and RIG have also been used for post-exposure prophylaxis for other lyssaviruses (Nel, 2005), notably ABLV (Fielding & Nayda, 2005). In cross-neutralization studies using human sera from persons vaccinated with human diploid-cell vaccine (HDCV), human antibodies prevented cell infection with ABLV and ELBV types 1 and 2 in a modified fluorescent antibody virus neutralization assay at titers $\geq 0.5 \, IU/ml$ (Fielding & Nayda, 2005). In experimental trials using PEP to treat Syrian hamsters and domestic ferrets, standard rabies biologicals demonstrated reduced, but offered some protection against heterologous challenge with the four newly described Eurasian bat lyssaviruses (Table I; ARAV, KHUV, IRKV, and WCBV) (Hanlon et al., 2005). The effectiveness of vaccine and RIG in animal models was "…inversely related to the genetic distance between the new isolates and traditional rabies virus," providing

no significant protection against WCBV, the most divergent of the four new bat lyssaviruses from rabies virus (Hanlon et al., 2005).

4.3 Rabies Epizootics and Human Exposure

The tracking and analysis of PEP delivered during successive epizootic and enzootic phases of wildlife rabies are required for understanding the risk of human and animal exposure to rabies from these reservoir hosts (Gordon, Krebs, Rupprecht, Real, & Childs, 2005). The number of human PEPs can remain at elevated levels in regions of the United States where counts of rabid raccoons have greatly diminished in post-epizootic temporal stages (Chang et al., 2002). It is unknown if this is a phenomenon of passive surveillance where the cost and effort to submit a sample for testing is perceived as high such that every sick reservoir species individual is presumed rabid and simply disposed of rather than tested. As data from New York State demonstrate (Table 3.2), the number of animals submitted for rabies testing from a county unit in the years following the first few years of infection declines substantially. The average number of reservoir host species tested per county per year does not appear to constitute an adequate surveillance strategy for measuring rabies intensity among the wildlife species population in a geographic area. In some cases, no reservoir species animals were tested from a county unit for several years. This can be deceptive to the public because when they see zero cases, they interpret the finding as evidence that the disease is no longer present. What may be readily overlooked is that if no animals are tested, then there can be no cases, even though enzootic transmission is indeed highly likely to be occurring in an immediate locality if susceptible populations are present.

5 EPIDEMIOLOGY OF HUMAN RABIES IN NORTH AMERICA AND EUROPE

Human rabies in North America and Europe is now a very rare disease. The history and molecular typing of rabies viruses from cases occurring from 1990–2010 in the United States, Europe, and Japan show that many individuals were exposed in another country (Malerczyk, Detora, & Gniel, 2011; Velasco-Villa et al., 2008). Analyses of human brain material from many imported rabies cases have implicated canine-associated rabies virus variants from countries in which the dog bite was received; imported human rabies in the United States and Europe will continue to occur until Asia and Africa achieve canine rabies control.

Wherever there is or was dog-to-dog transmission of canine rabies virus variants, human rabies cases are or were largely attributable to

TABLE 3.2 Public Health Surveillance Testing of Raccoons, the Reservoir Species, in New York State Over Time, According to Year of Invading Epizootic[a]

Yr of Infection (data from N = ___# of counties)	Average Positive Cases	# Pos. Range (SD)	Ave. # Tested	# Tested Range (SD)	Overall % Positive	Range of % Pos. [b]	Median Number	
							Positives	Tested
1st (53 counties)	22	2–42 (20)	63	22–104 (41)	35%	7–75 %	17	53
2nd (53 counties)	72	0–177 (105)	112	0–259 (146)	64%	0–91 %	54	79
3rd (50 counties)	23	0–57 (34)	37	0–86 (49)	61%	15–78 %	12	15
4th (44 counties)	8	0–20 (12)	18	0–46 (28)	43%	17–80 %	4	8
5th (32 counties)	7	0–21 (14)	14	0–28 (14)	52%	18–92 %	5	10
6th (18 counties)	7	0–21 (14)	14	0–28 (14)	50%	17–83 %	6	10
7th (6 counties)	6	4–8 (2)	8	5–11 (3)	71%	50–89%	6	9

[a]Data are from 1990–1996, as the raccoon rabies epizootic invaded northward throughout the state.
[b]The range of percent positive among samples tested is based only on data from counties from which >5 raccoons were tested throughout the year.

dog-bite exposure. From 1946, the year the Communicable Disease Center established its national rabies control program, to 1965, 236 cases of human rabies were reported from the United States, of which 70% of the cases were male, 51.3% were ≤15 years of age, and approximately 82% were attributed to dog exposures (Held, Tierkel, & Steele, 1967). Although the risk of rabies has changed substantially due to post-exposure prophylaxis, the age distribution of persons bitten by dogs in the United States is indistinguishable from that occurring in Asia and Africa (Wunner & Briggs, 2010).

Table 3.3 summarizes 111 human rabies cases occuring in the USA from 1960–2011. Over these 52 years, a strong seasonal trend is observed in that the highest number of cases occurs in July through September (Figure 3.7). As previously observed, males are over-represented, with 78 cases among 111 total (70%). The median age of cases was 29 with a range of 2 to 82 years of age. There were 27 cases due to canine rabies virus variants from other countries, including 10 from Mexico and 4 from the Philippines (Figure 3.8). Most of the naturally occurring human rabies cases (40 of 100) in North America from 1960–2011 have been due to variants of rabies virus maintained by insectivorous bats (Table 3.4)(Anderson et al., 1984; Feder, Jr. et al., 2012; Noah et al., 1998).

There has been an inability to elicit a history of animal bite or direct contact with a bat from the patient or family and friends of some human rabies cases due to insectivorous bats (Table 3.5). For example, bites were reported in 12 cases, direct contact with a bat was reported in 11, and a bat in the home or immediate vicinity was reported in 7; for the remaining 8 of 40 cases, no history of a bat or other animal contact could be elicited. The most likely explanation for the lack of history of a bat bite are that the individuals failed to report a bat encounter, perhaps due to perception that it was insignificant (Gibbons, Holman, Mosberg, & Rupprecht, 2002) or because the bat bite went unnoticed (Messenger et al., 2002) (Figures 3.5 and 3.6).

The genotype of rabies virus variants associated with the bat species *Perimyotis subflavus* (formerly *Pipistrellus subflavus*) (4–10 gm) and *Lasionycteris noctivagans* (P.s./L.n. variant) (8–10 gm), is the most frequent associated with human rabies due to bat variants in North America (Messenger, Smith, Orciari, Yager, & Rupprecht, 2003). Experimental evidence suggests that these viruses may have characteristics for enhanced transmission via superficial wounds at peripheral body sites (Dietzschold, Schnell, & Koprowski, 2005; Messenger et al., 2003; Morimoto et al., 1996). The observations that an unnoticed or trivial contact with bats may result in rabies transmission to humans has led to a recommendation that when a bat is physically present, a bite to an individual cannot be ruled out, and rabies cannot be ruled out through testing of the bat, PEP should be considered (Advisory Committee on Immunization Practices, 1999).

TABLE 3.3   Human Rabies Cases in the USA, 1960–2011

	Year	Month of Illness	Outcome	Age	Gender	State	RT-PCR Positive	Diagnostic Method(s)	Exposure Location	Source	Route	Variant
1	1960	5	died	9	M	GA	no sample	>Two	USA	Dog	Bite	Unknown
2	1960	8	died	19	F	OH	no sample	>Two	Guatemala	Cat	Unknown	Unknown
3	1961	1	died	53	F	KY	no sample	>Two	USA	Fox	Bite	Unknown
4	1961	1	died	76	M	CA	no sample	>Two	USA	Dog	Bite	Unknown
5	1961	6	died	74	M	KY	no sample	>Two	USA	Fox	Bite	Unknown
6	1962	7	died	3	M	TX	no sample	>Two	USA	Dog	Direct contact	Unknown
7	1962	10	died	11	M	ID	no sample	>Two	USA	Bat	Bite	Unknown
8	1963	8	died	52	F	AL	no sample	>Two	USA	Dog	Direct contact	Unknown
9	1964	8	died	10	M	MN	no sample	>Two	USA	Skunk	Bite	Unknown
10	1965	5	died	60	M	WV	no sample	>Two	USA	Dog	Bite	Unknown
11	1966	8	died	10	M	SD	no sample	>Two	USA	Skunk	Bite	Unknown
12	1967	7	died	58	F	NY	no sample	>Two	Guinea	Dog	Unknown	Unknown
13	1967	7	died	9	M	OR	yes	>Two	Egypt	Dog	Unknown	Dog, Old World
14	1968	8	died	14	M	KS	no sample	>Two	USA	Dog	Bite	Unknown
15	1969	4	died	2	M	CA	no sample	>Two	USA	Bobcat	Bite	Unknown
16	1970	7	died	11	M	AZ	no sample	>Two	USA	Skunk	Bite	Unknown
17	1970	7	died	4	M	SD	no sample	>Two	USA	Skunk	Bite	Unknown

18	1970	10	**Survived**	6	M	OH	no sample	>Two	USA	Bat	Bite	Unknown
19	1971	3	died	6	M	CA	no sample	>Two	USA	Unknown	Unknown	Unknown
20	1971	11	died	64	M	NJ	no sample	>Two	USA	Bat	Bite	Unknown
21	1972	3	died	70	M	CA	yes	>Two	Philippines	Dog	Unknown	Dog, Phillipines
22	1972	3	died	56	M	TX	no sample	>Two	USA	Aerosol	Laboratory accident	Vaccine strain
23	1973	9	died	26	M	KY	no sample	>Two	USA Bat	Bite	Bat, Perimyotis subflavus	
24	1975	1	died	60	M	MN	no sample	>Two	USA	Cat	Bite	Skunk, North-Central United States
25	1975	7	died	51	M	PR	no sample	>Two	USA, Puerto	Dog	Unknown	Unknown
26	1975	8	died	16	F	CA	yes	>Two	Mexico	Dog	Unknown	Dog, West Mexico/ United States
27	1976	6	died	55	F	MD	yes	>Two	USA	Bat	Bite	Bat, Perimyotis subflavus (Ps)
28	1976	8	died	17	M	TX	yes	>Two	Mexico	Dog	Unknown	Dog, Northeast Mexico/United States
29	1977	4	**Survived**	32	M	NY	no sample	>Two	USA	Aerosol	Laboratory accident	Vaccine strain (ERA)

(*Continued*)

TABLE 3.3   (Continued)

	Year	Month of Illness	Outcome	Age	Gender	State	RT-PCR Positive	Diagnostic Method(s)	Exposure			
									Location	Source	Route	Variant
32	1978	6	died	25	M	TX	yes	>Two	Mexico	Dog	Unknown	Dog, Northeast Mexico/United States
30	1978	7	died	39	M	OR	no sample	>Two	USA	Unknown	Unknown	Unknown
31	1978	9	died	37	F	ID	yes	>Two	USA	Corneal transplant	Transplant	Bat, Lasionycterus noctivagans (Ln)
33	1978	12	died	50	M	WV	no sample	>Two	USA	Unknown	Unknown	Unknown
34	1979	5	died	8	M	TX	yes	>Two	Mexico	Dog	Unknown	Dog, Northeast Mexico/United States
35	1979	6	died	7	F	TX	no sample	>Two	USA	Dog	Bite	Unknown
36	1979	7	died	37	M	CA	yes	>Two	Mexico	Dog	Unknown	Dog, West Mexico/United States
37	1979	9	died	24	M	OK	yes	>Two	USA	Unknown	Unknown	Bat, Perimyotis subflavus
38	1979	11	died	45	M	KY	yes	>Two	USA	Ground hog	Direct contact	Bat, Perimyotis subflavus
39	1981	7	died	27	M	OK	yes	>Two	USA	Unknown	Unknown	Skunk, South-Central United States

40	1981	9	died	40	M	AZ	yes	>Two	Mexico	Dog, Mexico	Unknown	Dog, West Mexico/United States
41	1983	1	died	30	M	MA	yes	>Two	Nigeria	Dog, Nigeria	Unknown	Dog, Nigeria
42	1983	3	died	5	F	MI	yes	>Two	USA	Bat	Bite	Bat, Lasionycterus noctivagans
43	1984	8	died	12	F	TX	yes	>Two	Laos	Dog	Unknown	Dog, Southeast Asia (Laos)
44	1984	9	died	12	M	PA	yes	>Two	USA	Unknown	Unknown	Bat, Myotis californicus
45	1984	10	died	72	F	CA	yes	>Two	Guatemala	Dog	Unknown	Dog, Mexico/ Guatemala
46	1985	5	died	19	M	TX	yes	>Two	Mexico	Dog	Unknown	Dog, Mexico City
47	1987	12	died	13	M	CA	yes	>Two	Philippines	Unknown	Unknown	Dog, Phillipines
48	1989	2	died	18	M	OR	yes	>Two	Mexico	Unknown	Unknown	Dog, Mexico
49	1990	6	died	22	M	TX	yes	>Two	USA	Bat	Bite	Bat, Tadarida brasiliensis
50	1991	8	died	55	F	TX	yes	>Two	USA	Unknown	Unknown	Dog/coyote, USA
51	1991	8	died	29	M	AR	yes	>Two	USA	Bat	Bite	Bat, L. nocyivagans/ P. subflavus

(*Continued*)

TABLE 3.3   (Continued)

	Year	Month of Illness	Outcome	Age	Gender	State	RT-PCR Positive	Diagnostic Method(s)	Exposure			
									Location	Source	Route	Variant
52	1991	10	died	27	F	GA	yes	>Two	USA	Unknown	Unknown	Bat, L. nocyivagans/ P. subflavus
53	1992	5	died	11	M	CA	yes	>Two	India	Dog	Bite	Dog, India
54	1993	7	died	11	F	NY	yes	>Two	USA	Unknown	Unknown	Bat, L. nocyivagans/ P. subflavus
55	1993	11	died	82	M	TX	yes	>Two	USA	Cow	Direct contact	Bat, L. nocyivagans/ P. subflavus
56	1993	11	died	69	M	CA	yes	>Two	Mexico	Dog	Bite	Dog, Mexico
57	1994	1	died	44	M	CA	yes	>Two	USA	Cat	Direct contact	Bat, L. nocyivagans/ P. subflavus
58	1994	6	died	40	M	FL	yes	>Two	Haiti	Dog	Unknown	Dog, Haiti
59	1994	10	died	24	F	AL	yes	>Two	USA	Unknown	Bat in vicinity	Bat, Tadarida brasiliensis
60	1994	10	died	41	M	WV	yes	>Two	USA	Bat	Bite	Bat, L. nocyivagans/ P. subflavus
61	1994	11	died	42	F	TN	yes	>Two	USA	Unknown	Unknown	Bat, L. nocyivagans/ P. subflavus

62	1994	11	died	14	M	TX	yes	>Two	USA	Dog	Direct contact	Dog/coyote, USA
65	1995	3	died	4	F	WA	yes	>Two	USA	Bat (likely)	Bat in home	Bat, Myotis sp.
63	1995	9	died	27	M	CA	yes	>Two	USA	Bat	Direct contact	Bat, Tadarida brasiliensis
66	1995	10	died	13	F	CT	yes	>Two	USA	Unknown	Bat in home	Bat, L. nocyivagans/ P. subflavus
64	1995	11	died	74	M	CA	yes	>Two	USA	Bat	Direct contact	Bat, L. nocyivagans/ P. subflavus
67	1996	2	died	26	M	FL	yes	>Two	Mexico	Dog	Bite	Dog, Mexico
68	1996	8	died	32	F	NH	yes	>Two	Nepal	Dog	Bite	Dog, Southeast Asia (Nepal)
69	1996	10	died	42	F	KY	yes	>Two	USA	Unknown	Unknown	Bat, L. nocyivagans/ P. subflavus
70	1996	12	died	49	M	MT	yes	>Two	USA	Bat (likely)	Bat in vicinity	Bat, L. nocyivagans/ P. subflavus
71	1997	1	died	65	M	MT	yes	>Two	USA	Bat (likely)	Bat in vicinity	Bat, L. nocyivagans/ P. subflavus
72	1997	1	died	71	M	TX	yes	>Two	USA	Bat	Direct contact	Bat, L. nocyivagans/ P. subflavus

TABLE 3.3   (Continued)

	Year	Month of Illness	Outcome	Age	Gender	State	RT-PCR Positive	Diagnostic Method(s)	Exposure			
									Location	Source	Route	Variant
73	1997	10	died	32	M	NJ	yes	>Two	USA	Bat	Direct contact	Bat, L. nocyivagans/ P. subflavus
74	1997	10	died	64	M	WA	yes	>Two	USA	Unknown	Bat in vicinity	Bat, Eptesicus fuscus
75	1998	12	died	29	M	VA	yes	>Two	USA	Unknown	Bat in vicinity	Bat, L. nocyivagans/ P. subflavus
76	2000	9	died	47	M	MN	yes	>Two	USA	Bat	Bite	Bat, L. nocyivagans/ P. subflavus
77	2000	9	died	54	M	NY	yes	>Two	Ghana	Dog	Bite	Dog, A frica (Ghana)
78	2000	10	died	49	M	CA	yes	>Two	USA	Bat	Direct contact	Bat, Tadarida brasiliensis
79	2000	10	died	26	M	GA	yes	>Two	USA	Bat	Direct contact	Bat, Tadarida brasiliensis
80	2000	10	died	69	M	WI	yes	>Two	USA	Bat	Direct contact	Bat, L. nocyivagans/ P. subflavus
81	2001	2	died	72	M	CA	yes	>Two	Philippines	Unknown	Unknown	Dog, Phillipines

82	2002	3	died	28	M	CA	yes	>Two	USA	Bat	Direct contact	Bat, L. nocyivagans/ P. subflavus
83	2002	8	died	13	M	TN	yes	>Two	USA	Bat	Direct contact	Bat, Tadarida brasiliensis
84	2002	9	died	20	M	IA	yes	>Two	USA	Unknown	Unknown	Bat, L. nocyivagans/ P. subflavus
85	2003	2	died	25	M	VA	yes	>Two	USA	Unknown	Unknown	Raccoon, eastern US
86	2003	5	died	64	M	PR	yes	>Two	USA, Puerto	Dog	Bite	Dog/mongoose, Puerto Rico
87	2003	8	died	66	M	CA	yes	>Two	USA	Bat	Bite	Bat, L. nocyivagans/ P. subflavus
88	2004	2	died	41	M	FL	yes	>Two	Haiti	Dog	Bite	Dog, Haiti
89	2004	4	died	20	M	AR	no sample	>Two	USA	Bat	Bite	Bat, Tadarida brasiliensis
90	2004	5	died	53	M	OK	yes	>Two	USA	Organ transplant	Transplant	Bat, Tadarida brasiliensis
91	2004	5	died	50	F	TX	yes	>Two	USA	Organ transplant	Transplant	Bat, Tadarida brasiliensis
93	2004	5	died	18	M	TX	yes	>Two	USA	Organ transplant	Transplant	Bat, Tadarida brasiliensis

(Continued)

TABLE 3.3   (Continued)

	Year	Month of Illness	Outcome	Age	Gender	State	RT-PCR Positive	Diagnostic Method(s)	Exposure			
									Location	Source	Route	Variant
92	2004	6	died	55	F	TX	yes	>Two	USA	Artery transplant	Transplant	Bat, Tadarida brasiliensis
94	2004	10	**Survived**	15	F	WI	**neg**	>Two	USA	Bat	Bite	no isolate
95	2004	10	died	22	M	CA	yes	>Two	El Salvador	Unknown	Unknown	Dog, El Salvador
96	2005	9	died	10	M	MS	no sample	>Two	USA	Bat	Direct contact	no isolate
97	2006	5	died	16	M	TX	yes	>Two	USA	Bat	Direct contact	Bat, Tadarida brasiliensis
98	2006	9	died	10	F	IN	yes	>Two	USA	Bat	Bite	Bat, Lasionycterus noctivagans
99	2006	11	died	11	M	CA	yes	>Two	Philippines	Dog	Bite	Dog, Phillipines
100	2007	9	died	46	M	MN	yes	>Two	USA	Bat	Bite	Bat, L. nocyivagans/ P. subflavus
101	2008	3	died	16	M	CA	yes	>Two	Mexico	Fox	Bite	Bat, Mexico, new Tb
102	2008	11	died	55	M	MO	yes	>Two	USA	Bat	Bite	Bat, Lasionycterus noctivagans
103	2009	2	**Survived**	17	F	TX	**neg**	IFA only	USA	Unknown	Unknown	no isolate

104	2009	10	died	43	M	IN	yes	>Two	USA	Unknown	Bat in vicinity	Bat, Perimyotis subflavus
105	2009	10	died	42	M	VA	yes	>Two	India	Dog	Direct contact	Dog, India
106	2009	10	died	55	M	MI	yes	>Two	USA	Bat	Direct contact	Bat, Lasionycterus noctivagans
107	2010	8	died	19	M	LA	yes	>Two	Mexico	Bat	Bite	Bat, Mexico, Desmodus rotundus
108	2010	12	died	70	M	WI	yes	>Two	USA	Unknown	Unknown	Bat, Perimyotis subflavus
109	2011	4	**Survived**	8	F	CA	**neg**	IFA only	USA	Unknown	Unknown	no isolate
110	2011	7	died	73	F	NJ	yes	>Two	Haiti	Dog	Bite	Dog, Haiti
111	2011	8	died	24	M	NY	yes	>Two	Afghanistan	Dog	Bite	Dog, Afghanistan

FIGURE 3.7   Monthly occurrence of human rabies cases in the USA, 1960–2011.
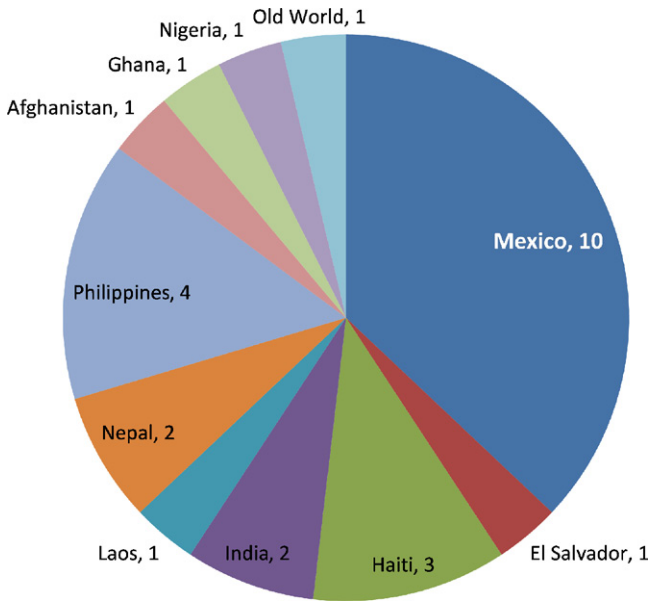

FIGURE 3.8   Human rabies cases in the USA due to canine rabies virus variants from other countries, 1960–2011.

Due to the relative rarity of human rabies cases in some countries, clinical suspicion of rabies can be low and only recognized postmortem when infected material from the index patient is transpanted into recipient patients (Centers for Disease Control and Prevention, 2004; Maier

TABLE 3.4 Variant and RT-PCR Test Status of 111 Human Rabies Cases in the USA, 1960–2011

Rabies Virus Variant	Number of Cases
Lasionycteris noctivagans/Perimyotis subflavus	32
Tadarida brasiliensis	13
Eptescus fuscus	1
Myotis californicus	1
Desmodus rotundus	1
Myotis sp.	1
Total bat cases	49
Dog, imported cases	27
Dog/coyote, USA	2
Skunk	2
Dog/mongoose, Puerto Rico	1
Raccoon	1
Laboratory strain (accidental infection)	2
Total other cases	35
RT-PCR (or variant determination) test status	
No sample for PCR testing	29
RT-PCR positive	79
RT-PCR negative	3
Total	111

et al., 2010). Numerous cases of human rabies have been detected only through postmortem examination of formalin-fixed brain tissue (Noah et al., 1998) or, less frequently, analysis of serum and cerebrospinal fluid for rising antibody titers to rabies virus that neutralize virus as measured by the rapid fluorescent focus inhibition test (RFFIT)(Lewis, 2007; Feder, Jr. et al., 2012). A 2005 case of rabies in a Mississippi resident (Figure 3.9; Table 3.3) was diagnosed retrospectively on the basis of detection of rabies virus-specific antibodies by both RFFIT and the indirect fluorescent antibody (IFA) test (Centers for Disease Control and Prevention, 2006; Lewis, 2007). The diagnosis of rabies in humans, particularly antemortem, and also postmortem when samples from the patient may be limited, can be challenging. A battery of tests is necessary. Ante- and postmortem diagnostic methods have varied through the years, but current approaches consist of detection of neutralizing antibody in serum, cerebrospinal fluid (CSF),

TABLE 3.5 Exposure History of Naturally Occurring Human Rabies Cases in the USA due to Bat-Associated Rabies Virus Variants, 1960–2011

Species of Bat with which the Rabies Virus Variants in Human Cases are Associated[a]	Bite	Direct Contact	Bat in Home/ Vicinity	Unknown	Number of cases
Lasionycteris noctivagans/ Perimyotis subflavus	10	6	5	7	28
Tadarida brasiliensis	2	5	1	0	8
Eptescus fuscus	0	0	1	0	1
Myotis sp.	0	0	1	1	2
Desmodus rotundus (Mexico)	1	0	0	0	1
Total	13	11	8	8	40

[a]*Excludes a total of nine bat-associated rabies virus variant cases which occurred in the USA; four cases of rabies due to Lasionycteris noctivagans/Perimyotis subflavus virus variant with one occurring after a corneal transplant and one each following direct contact with a cow, cat, and groundhog; one case of a Tadarada brasiliensis-like variant following a fox bite in Mexico; and four cases of rabies due to the Tadarida brasiliensis rabies virus variant following organ or vascular graft transplantation.*
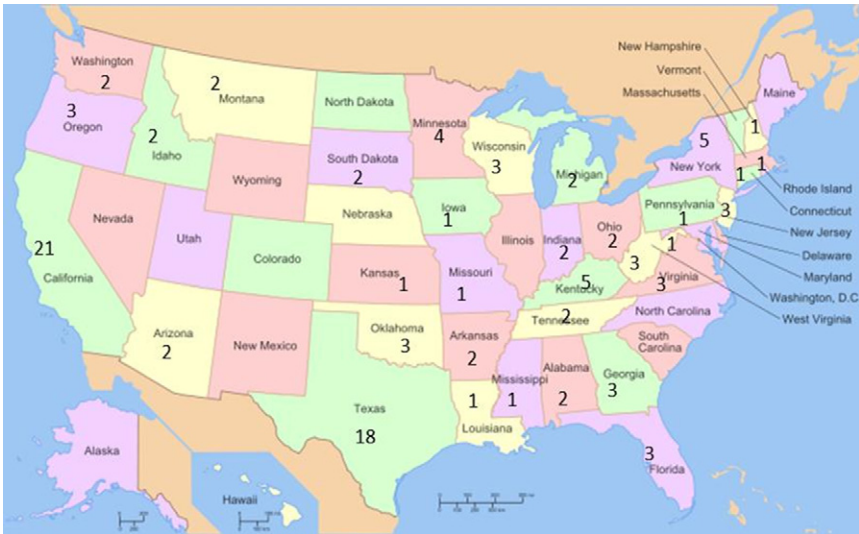

FIGURE 3.9 **Human rabies cases in the United States, 1960–2011, by geographic occurrence.**

and sometimes other body fluids by the rapid fluorescent focus inhibition test (RFFIT), detection of binding antibody by an indirect fluorescent antibody (IFA) test, antigen detection in various samples (i.e., skin, brain, etc.) with direct fluorescent antibody reagents and monoclonal antibodies,

and genome detection by reverse transcription polymerase chain reaction (RT-PCR) assay most often on saliva or brain material. Often, sequential sampling from suspect patients is necessary (Feder, Jr. et al., 2012).

The RT-PCR diagnostic method is exquisitely sensitive. Of the 111 cases reviewed in Table 3.3, 79 had positive findings, although no samples were available for testing from 29 cases. Only 3 cases had negative RT-PCR findings. The first of these cases was the Wisconsin teenager (Figure 3.9; Table 3.3) with virus neutralizing antibody in CSF on the first day of hospitalization. Subsequent sampling revealed increasing neutralizing titers in CSF and serum, but IFA findings were only positive in serum (Feder, Jr. et al., 2012). These findings, along with a high index of suspicion of rabies upon admission to hospital and novel, proactive supportive treatment appears to have contributed to the survival and positive outcome for this patient (Willoughby, Jr. et al., 2005). In contrast, the remaining two cases with RT-PCR negative findings were diagnosed solely on the IFA diagnostic method (Centers for Disease Control and Prevention, 2010; Centers for Disease Control and Prevention, 2012). No neutralizing antibody activity was detected in either patient's serum or CSF, and no rabies virus antigen was detected in skin biopsies. The 2009 Texas case (Figure 3.9; Table 3.3) never required intensive care. Considering the rapid recovery from clinical illness and no neurologic sequelae in these two cases of "survival from rabies," it would seem that further investigation of the source and interpretation of the finding of binding antibodies by IFA would be warranted. Moreover, these methods for diagnosis of rabies in humans are not under the jurisdiction of CLIA but rather are more appropriately considered experimental. Each method as it is applied in unique laboratories requires validation and periodic scrutiny to optimize test performance characteristics.

Although the raccoon rabies epizootic has been one of the most intensive and extensive wildlife epizootics ever recorded, involving 100,000s of animals affected by spillover of this variant (Childs et al., 2000; Gordon et al., 2005), only a single human rabies death has been attributed to this particular variant (Centers for Disease Control and Prevention, 2003). From 1960–2011, two cases of human rabies due to skunk rabies virus variants have been diagnosed in the United States (Tables 3.3 and 3.4). The last human case attributable to exposure to a rabid fox was in Kentucky in 1961 (Anderson et al., 1984).

6 EPIDEMIOLOGY OF HUMAN RABIES IN AFRICA AND ASIA

The vast majority of all human rabies deaths occur in the developing countries where canine rabies virus variants continue to circulate extensively (World Health Organization, 2005). The geographic area of the

tropics has accounted for more than 99% of human deaths and ~90% of PEP for rabies (Acha & Arambulo, 1985). Although most rabies deaths are reported from urbanized areas where dog and human populations reach their highest population densities (Beran, 1982), the rate of bites and risk of infection is greater in rural locations. Overall estimates of the annual incidence of bites received from suspect rabid dogs are 100 per 100,000 persons in urban and rural settings in Africa and 100 and 120, respectively, for persons in rural and urban settings in Asia (Cleaveland, Kaare, Tiringa, Mlengeya, & Barrat, 2003; Knobel et al., 2005; Meslin, 2005).

Rabies in Africa and Asia disproportionately afflicts residents in areas of lower socio-economic status in rural and urban settings (Fagbami, Anosa, & Ezebuiro, 1981; Knobel et al., 2005). The estimated direct and indirect costs of rabies PEP is US $39.57 in Africa and US $49.41 in Asia, which represents approximately 5.8% and 3.4% of the annual income for the average person in Africa and Asia, respectively (Knobel et al., 2005). Rabies epizootics among dogs in cities may continue for longer periods in areas of lower socio-economic status (Eng et al., 1993), in part due to the large populations of free-roaming dogs, lack of adequate vaccination coverage of owned or neighborhood dogs, and the lack of resources available for timely control of epizootics (Wilde et al., 2005). Even within the United States, more severe problems associated with higher densities of free-ranging dogs occur in economically challenged urban neighborhoods (Beck, 1975).

In most areas of the world, accurate estimates of human rabies deaths are impossible to obtain as surveillance systems and regional laboratories are inadequate or nonexistent for the systematic detection and laboratory confirmation of human or animal rabies cases. The proportion of rabies cases detected and reported to the WHO in 1999 was estimated to represent only 3% of the total global rabies mortality (Knobel et al., 2005). Novel methods of estimating human rabies deaths have focused on extrapolations from studies estimating domestic dog population densities in different regions in Africa and Asia (Childs et al., 1998), or directly from the incidence of dog-bite in African countries, such as Uganda and Tanzania (Cleaveland, Fevre, Kaare, & Coleman, 2002; Fevre et al., 2005). Risk models based on the likelihood of clinical rabies developing after being bitten by a rabid dog suggest that some 55,000 (90% confidence interval = 24,000–93,000) human rabies deaths occur annually in Africa and Asia (Knobel et al., 2005).

Dog-associated rabies has increased throughout most of sub-Saharan Africa during the last 70 years, although it remains difficult to assess the magnitude of rabies deaths in countries without adequate surveillance or laboratory facilities in the region. In 1997, laboratory confirmation of rabies was available for less than 0.5% of the estimated human rabies cases (World Health Organization, 2005). Sensitive, specific, and, perhaps

most important, widely available laboratory testing is an essential element for surveillance for rabies—as is the case with any disease.

7 THE BURDEN AND COST OF RABIES IN AFRICA AND ASIA

An additional health burden to that directly resulting from rabies mortality is the high percentage of adverse reactions to PEP involving nerve tissue origin vaccines. An estimated 200,000 persons in Africa and 7,500,000 persons in Asia (India, China, and other southeastern Asian nations) annually receive PEP for rabies exposures (Knobel et al., 2005). Of those individuals receiving Semple type vaccines, derived from phenol-treated sheep- or goat-brain tissue (Swaddiwuthipong, Weniger, Wattanasri, & Warrell, 1988), or those receiving vaccines derived from suckling-mouse brain tissue (Held & Adaros, 1972), an estimated 360 (CI = 142–586) and 44,525 (CI = 17,585–72,575) disability-adjusted life years (DALY) are lost annually due to adverse reactions among individuals treated in Africa and Asia, respectively (Knobel et al., 2005). The proportion of neuroparalytic complications among persons receiving brain tissue vaccines have been estimated at between 0.3 to 0.8 adverse reactions per 1,000 vaccinees (World Health Organization, 2005).

The global public health cost of rabies is far in excess of metrics limited to the loss of human life. Estimates of the annual burden of canine rabies in Africa and Asia, based on direct medical expenses and costs incurred by patients seeking treatment, amount to US \$20.5 million (CI = 19.3–21.8) and US \$563 million (CI = 520–605.8), respectively (Knobel et al., 2005). In local studies, such as in Thailand, an estimated >200,000 persons received PEP with cell-culture-derived vaccines in 1997 at a cost of approximately US \$10 million (Knobel et al., 2005).

8 EPIZOOTIOLOGY OF RABIES IN LATIN AMERICA

Reports of human rabies deaths in Latin America are substantially lower than rates in Asia and Africa. In large part, the declining rates in Latin America reflect a highly effective regional program of dog rabies control (Organización Panamericana de la Salud (OPS), 1983). Nonetheless, dog-associated rabies remains the principal source of human rabies throughout Latin America. During the interval between 1993 and 2002, 65.2% of the 1,147 human deaths recorded were associated with dogs (Belotto, Leanes, Schneider, Tamayo, & Correa, 2005). In

Mexico, where vampire bat and dog rabies variants co-occur, dog exposures account for ~81% of human rabies deaths (mainly urban) and vampire bats account for ~11% of cases (mostly rural)(de Mattos et al., 1999).

As in Mexico, rabies occurring among domestic animals and humans in Brazil is either of vampire bat origin or associated with dogs (Ito et al., 2003), irrespective of the presence of other variants circulating among other species of bats (Kobayashi et al., 2005).

On islands in the Caribbean, dog-variants of rabies viruses have become established within introduced populations of mongooses and mongooses are responsible for sporadic cases of human rabies such as reported from Puerto Rico (Krebs, Mandel, Swerdlow, & Rupprecht, 2005).

Detailed information on rabies virus variants circulating among sylvatic animal reservoirs is becoming available from Mexico (de Mattos et al., 1999; Velasco-Villa et al., 2002; Velasco-Villa et al., 2005; Velasco-Villa et al., 2008) and several South American countries, such as Bolivia (Favi, Nina, Yung, & Fernandez, 2003), Brazil (Bordignon et al., 2005; Schaefer, Batista, Franco, Rijsewijk, & Roehe, 2005; Shoji et al., 2006), Chile (de Mattos, Favi, Yung, Pavletic, & de Mattos, 2000; Favi, Bassaletti, Lopez, Rodriguez, & Yung, 2011; Favi et al., 2002; Yung, Favi, & Fernandez, 2012), and Colombia (Paez, Nunez, Garcia, & Boshell, 2003; Paez, Saad, Nunez, & Boshell, 2005). In Brazil, molecular sequence data based on the rabies virus N gene have identified four rabies virus variants clustering with four bat genera; one lineage is associated with the common vampire bat, *Desmodus rotundus*, the other three segregate with three families/genera of insectivorous bats, *Eptesicus*, *Molossus*, and *Nyctinomops* (Kobayashi et al., 2005, 2007). A novel variant of rabies isolated from marmosets (*Callithix jacchus*) in Brazil was linked to a human rabies case (Favoretto, de Mattos, Morais, Alves Araujo, & de Mattos, 2001). Rare human rabies deaths in Chile, Colombia, and Brazil have been attributed to rabies virus variants circulating in insectivorous bats (Favi et al., 2002; Paez et al., 2003). In Colombia, variants of rabies virus detected from a case of human rabies and three cases of dog rabies indicated infection by bat-associated variants of rabies virus circulating in two species *Eptesicus brasiliensis* and *Molossus molossus* (Paez et al., 2003). The domestic dog variant of rabies virus appears to have successfully established enzootic maintenance among gray foxes (*Urocyon cineroargenteus*) in Colombia (Paez et al., 2005).

In Mexico, where human rabies is associated with vampire bat and canine rabies virus variants, a newly identified rabies virus variant present among skunks (species not identified) and distinguishable from those rabies virus variants circulating among skunks in North America has been identified (de Mattos et al., 1999).

8.1 Vampire Bat Rabies and Epizootic Cycles of Bovine Rabies

The association of vampire bats and rabies epizootics among cattle in Latin America was first noted in 1910 in Brazil (Carini, 1911). The first human deaths attributed to bites received from vampire bats were documented on the Island of Trinidad (Carini, 1911; Hurst & Pawan, 1959), where vampire bat transmitted rabies continues to be a sporadic disease of cattle (Carini, 1911; Wright, Rampersad, Ryan, & Ammons, 2002). Outbreaks of human rabies due to vampire bats continue to be reported from many South and Central American countries and rabies virus variants originating from vampire bats continue to be isolated from cattle and other species in Argentina (Carini, 1911; Cisterna et al., 2005; Wright et al., 2002), Bolivia (Carini, 1911; Favi et al., 2003; Wright et al., 2002), Brazil (Batista-da-Costa, Bonito, & Nishioka, 1993; Carini, 1911; Ito et al., 2001; Kobayashi et al., 2008; Wright et al., 2002), Peru (Lopez, Miranda, Tejada, & Fishbein, 1992), Venezuela (Caraballo, 1996), Costa Rica (Badilla et al., 2003), Colombia (Badillo, Mantilla, & Pradilla, 2009), and Mexico (de Mattos et al., 1999; Martinez-Burnes et al., 1997).

Vampire bats feed preferentially on livestock. In addition to compromising animal productivity, vampire bats present a significant economic burden through losses due to rabies (Baer, 1991; Delpietro & Russo, 1996; Martinez-Burnes et al., 1997). The use of anticoagulants, applied by topical treatment to the backs of captured bats, subsequently released to return to roosting sites (Linhart, Flores, & Mitchell, 1972), or through systemic treatment of cattle, have been used to achieve reductions in vampire bat biting rates on cattle of 85 to 96% (Flores, Said, De Anda, Ibarra, & Anaya, 1979). Unfortunately, vampire bat control also leads to the death of many non-target species of bats (Mayen, 2003).

The migratory wave of vampire bat rabies has been estimated to travel at 40 to 50 km per year (Brass, 1994), remarkably similar to the rates (30–60 km per year) established for the spread of red fox and raccoon rabies epizootics (Wandeler, 2004; Lucey et al., 2002). Cyclic changes in vampire bat populations could drive cyclic and periodic epizootics of cattle rabies caused by vampire bat transmitted rabies. In regions of Central and South America, areas affected by vampire rabies experience outbreaks every 2 to 3 years (Ruiz & Chavez, 2010).

9 CASE NUMBER DYNAMICS AND MODELING

Rabies epizootics among wildlife reservoir host populations within defined regions frequently follow a distinct course. Intervals of increased disease activity (epizootics) are separated by intervals (inter-epizootics) in which rabies may seem to disappear or reach undetectable

levels within a local mammalian community (Anderson, Jackson, May, & Smith, 1981; Childs et al., 2000; Steck & Wandeler, 1980; Wandeler et al., 1974). Following an initial epizootic of rabies, which is typically the largest of a possible series of epizootics that may emerge over time as wildlife rabies enters into a new region to infect previously naive populations, a series of successively smaller epizootics may occur at increasing frequency over time (Anderson et al., 1981; Coyne, Smith, & McAllister, 1989; Smith et al., 2002). The periodic epizootic structure of rabies epizootics may become indistinguishable against a background level of disease. Primary data from New York State during the initial invasion of the raccoon rabies epizootic, reveal the weaknesses of wildlife rabies surveillance based on a passive public health system (Table 3.2). With an estimated average raccoon population in the affected counties, testing fewer than one suspect raccoon per month per county is a poor indicator of the intensity of rabies among the susceptible population and most likely underestimates the risk to domestic animals and humans.

Despite the limitations of a passive surveillance system intended solely for public health purposes, rabies virus maintenance in animal reservoirs and related data have served as a model system for illustrating many important concepts in infectious disease epidemiology and the theoretical modeling of the population biology of a virus and its host. Predictions from model outcomes have been used to identify temporal linkages in the risk of rabies virus spillover from sylvatic reservoirs to domestic species and other wildlife (Gordon et al., 2004; Guerra et al., 2003), the design of rational intervention schemes based on geographic simulators projecting rabies spread following breaches in oral wildlife vaccination zones (Russell, Smith, Childs, & Real, 2005), and the development of analytic methods to inform economic models with finer scale resolution of cost structures associated with different temporal stages of rabies epizootics, providing improved estimates of the savings potentially accrued through active interventions (Gordon et al., 2005).

9.1 Red Fox Rabies

Beginning in the 1940s, an epizootic of red fox rabies began spreading from Russia and Poland towards Western Europe, eventually affecting much of the continent (Steck & Wandeler, 1980; Wandeler, 2008). The epizootic front of red fox rabies in Europe advanced in an irregular wave-like fashion at an estimated 25–60 km per year (Steck & Wandeler, 1980; Wandeler, 2004). From 1978 to 1999, over 151 million vaccine-laden baits were distributed in 18 European countries, which has greatly reduced and even eliminated fox rabies from many previously affected regions (Wandeler, 2008).

Areas of high quality habitat supporting high population densities of red foxes suffer the greatest population depression due to rabies and the highest incidence of disease during the initial epizootic, as based on hunter index estimates of red fox population size (Steck & Wandeler, 1980). Based on population estimates from hunter indeces, rabies reduced populations of red foxes in numbers to 50–60% below pre-epizootic levels (Bogel, Arata, Moegle, & Knorpp, 1974). Estimates of the time in years to recovery of fox populations to pre-rabies densities illustrate how high reproductive rates among these carnivores can rapidly increase densities above the minimum values required to sustain periodic reemergence of disease outbreaks (Bogel et al., 1974; Macdonald & Bacon, 1982).

Prevalence is a difficult attribute to estimate for wildlife disease such as rabies, as the required denominator (the population at a specific time or average population size during an interval of time) is almost never known. However, theoretical estimates and reported estimates from hunter indices of the equilibrium prevalence of rabies suggest the value remains fairly constant at 3–7% during outbreaks (Anderson et al., 1981; Bogel et al., 1974).

9.2 Fox Rabies

Arctic fox rabies virus variants have a near circumpolar distribution, and these fox virus variants remain an occasional source of human rabies in Asia (Kuzmin, 1999; Kuzmin, Hughes, Botvinkin, Gribencha, & Rupprecht, 2008; Shao et al., 2011). These variants were the source for independent cycling of rabies virus among raccoon dogs in Europe and Asia (Bourhy, Dacheux, Strady, & Mailles, 2005; Bourhy et al., 1999; Potzsch et al., 2006).

In North America, a major epizootic of the Arctic fox variant of rabies virus, involving red and arctic foxes (*Alopex lagopus*), began in northern Canada in the 1940s (Tabel, Corner, Webster, & Casey, 1974). In the early 1960s, the epizootic of red fox rabies expanded from Ontario into the northeastern states of New York, New Hampshire, Vermont, and Maine. Red fox rabies and spillover to domestic and wild animals in the United States occurred until the mid-1990s (Gordon et al., 2004), when effective control efforts initiated in Canada brought the fox rabies under control in neighboring Ontario (MacInnes et al., 2001), and coincidently resulted in the disappearance of red fox-associated rabies in the northeastern United States.

The first recorded case of rabies in foxes in the United States occurred in a gray fox (*U. cinereoargenteus*) in Georgia in 1940 (MacInnes et al., 2001). Within years, rabies was endemic among gray foxes in Alabama, Florida, and Tennessee, and from 1940 to 1960 gray and red foxes were the wild carnivore most commonly reported rabid in the United States. Since the 1940s, the endemic area affected by the gray fox-associated variant of rabies virus has diminished in size such that endemic gray

fox rabies in the United States is presently known only from relatively small areas in Texas and Arizona (Figure 3.2) (Rohde, Neill, Clark, & Smith, 1997). However, a phylogenetically related virus has been recovered from bobcats in Mexico (de Mattos et al., 1999), suggesting that this rabies virus variant may have a more extensive range than previously appreciated.

10 SKUNK RABIES VIRUS VARIANTS

Rabies among skunks has a long history in North America. The earliest reports of rabies from California in 1826 incriminate spotted skunks (genus *Spilogale*) as the source of human disease (Parker, 1975). Three genera of skunks occur in North American; these are *Mephites*, the striped skunk, and *Conepatus*, the hog-nosed skunks, and *Spilogale*. The striped skunk is by far the most common (Parker, 1975). Currently, two rabies virus biotypes, the South-Cental and North-Central biotypes, circulate among skunks in the central United States (Figure 3.2), with the North-Central Skunk biotype extending into central and western Canada; a third biotype of rabies virus circulates among skunks in California (Crawford-Miksza, Wadford, & Schnurr, 1999). Beginning in the 1960s and continuing until 1990 (Figure 3.10), skunks were the group of terrestrial mammals most frequently reported rabid in the United States.

In the United States and Canada, skunk rabies is common in prairie habitats (Greenwood, Newton, Pearson, & Schamber, 1997; Pool & Hacker, 1982), where periodically epizootic disease has been postulated to be a major factor in driving the cyclic variations in skunk population numbers (Pybus, 1988). The potential impact of rabies on skunk populations was amply demonstrated by Greenwood et al., (1997) who followed a population of radio-collared animals during an epizootic in South Dakota. Estimated rates of skunk density fell from 0.85 skunks per km^2 during April to June, 1991, to 0.17 skunks per km^2 in April to July, 1992, during the rabies epizootic.

11 RACCOON RABIES IN NORTH AMERICA

The epizootic associated with raccoons in the eastern United States is believed to have been initiated in the mid-Atlantic region by the interstate translocation of raccoons incubating rabies from an established focus of raccoon rabies in the southeastern USA for the purpose of restocking dwindling local populations (Nettles, Shaddock et al., 1979; Smith, Sumner et al., 1984). Since the mid-1970s, this raccoon-adapted variant of rabies virus has spread north to Maine and Ontario, Canada,
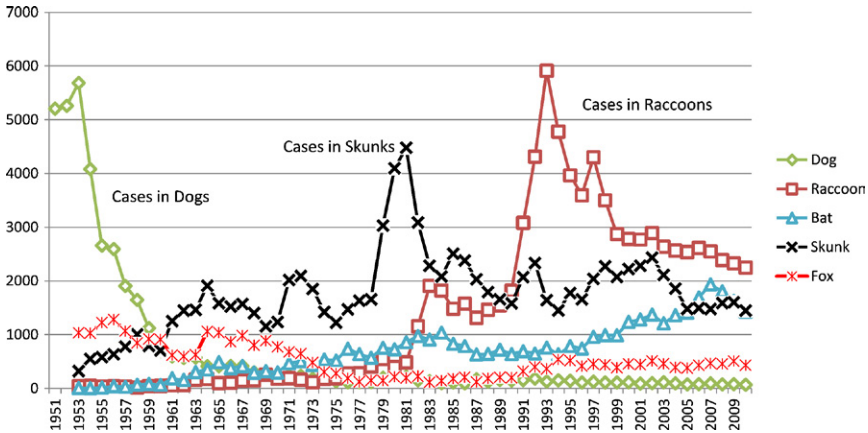
FIGURE 3.10 **Rabies diagnosed in select animals that are reservoir hosts for rabies in the USA, 1951–2010.**

and west to Ohio, causing one of the most intensive outbreaks of animal rabies ever recorded (Childs et al., 2000). Raccoons have been the wild animal species most frequently diagnosed as rabid since the early 1990s (Figure 3.10).

The magnitude of this epizootic was enhanced by the spread of virus through naive raccoon populations of very high density, often in states that had not experienced terrestrial rabies for decades (Hanlon et al., 1998). The interval from the start date of the initial epizootic as raccoon rabies enters a previously unaffected area, and the start date of the second epizootic, as defined by a statistical algorithm (Childs et al., 2000) obtained from time series data from the eastern United States, was 48 months.

There are no published estimates for the critical threshold value of the raccoon population density required to support rabies transmission in areas of the United States. However, direct and indirect estimates of raccoon population size or density indicate significant declines in population size following epizootics of raccoon rabies (Anthony et al., 1990). The magnitude of recorded epizootics, as well as the number of animals tested for possible rabies infection, is correlated with the human population size or density at the level of township and county (Gordon et al., 2005).

The local rate of disease propagation is significantly affected by local environmental heterogeneities, such as those posed by major rivers running orthogonal to the major direction of raccoon rabies spread. In Connecticut, models using a stochastic simulator determined the reduction in local transmission of raccoon rabies to be sevenfold for townships separated by a major river compared to townships without such a physical barrier (Smith et al., 2002). Habitat variation affecting the equilibrium raccoon population density appears to have an influence on the

rate of spread of raccoon rabies, as estimated by empirical data on the date of first appearance of rabies in townships of New York State and simulations of the expected rate of rabies spread (Russell, Smith, Waller, Childs, & Real, 2004). Coincident with the rabies wavefront reaching the Adirondack Mountains, advancement of the raccoon epizootic slowed approximately 4 years after entering New York State from the south in 1991. The population density of raccoons in this region of coniferous forests is extremely low (Godin, 2012). The Adirondack region continues to be a formidable barrier to raccoon rabies through 2010 (Blanton et al., 2011), and raccoon rabies has, for the most part, gone around rather than through this region into Canada.

Raccoon rabies was first detected in Ontario, Canada, in 1999, from across the St. Lawrence River border with the United States (Wandeler & Salsberg, 1999). Molecular epidemiologic analyses of raccoon variants from Canada indicate that three independent incursions of raccoon rabies have occurred—two in 1999 in Ontario, and one in 2000 in New Brunswick (Nadin-Davis, Muldoon, & Wandeler, 2006). More recently, confirmed positive raccoon-variant cases in southern Quebec have led to extensive efforts including local depopulation, trapping, and parenteral vaccination and vaccines offered in baits to try to control the incursion (Sterner, Meltzer, Shwiff, & Slate, 2009).

11.1 Rabies Virus Spillover to Domestic Dogs and Cats

With the effective implementation of dog vaccination, spillover of wildlife variants of rabies virus to dogs has declined in North America and Europe to levels below that reported for cats. Thus, in the 1990s, cats have replaced dogs as the companion animal species most commonly reported rabid. In the United States, the annual number of dog rabies cases, primarily due to spillover from rabies virus variants circulating among terrestrial wildlife, has fallen below 100, whereas the average number of cat cases is close to 300 per year (Figure 3.11). In southern Texas, a number of domestic dogs were infected with a dog/coyote variant of rabies virus in the 1990s. However, an aggressive vaccination campaign, both parenteral for dogs and targeted wildlife vaccination, appears to have successfully controlled this variant (Sidwa et al., 2005).

The majority of rabid cats are reported from the eastern United States, where the raccoon-adapted variant of rabies virus is endemic. The large and disproportionate number of rabid cats being identified in the United States presumably reflects poorer vaccine coverage in this animal than is achieved for dogs (Nelson, Mshar, Cartter, Adams, & Hadler, 1998). Required vaccination for cats is still not legally mandated in some states or counties. In 1996, a survey of the 50 states, the District of Columbia, and 3 of 5 territories revealed that 74% of these political units required
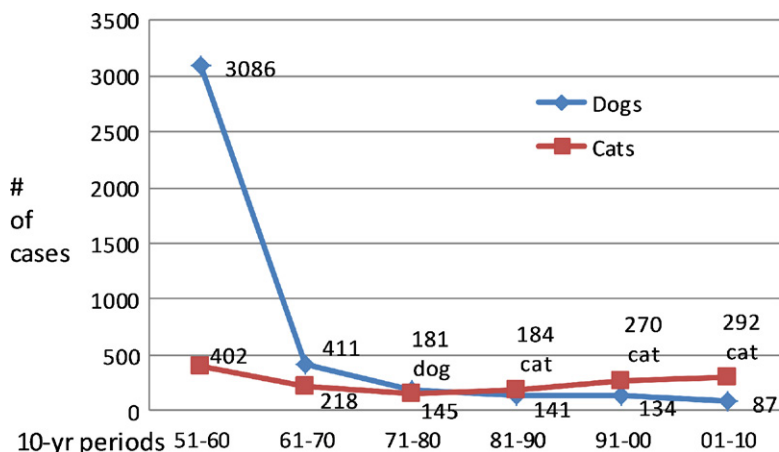
FIGURE 3.11   **Ten-year average number of cases of rabies diagnosed in dogs and cats in the USA, 1951–2010.**

dog vaccination compared with 52% requiring cat vaccination (Johnston & Walden, 1996). The large number of stray and unvaccinated cats has contributed greatly to the increase in rabies in this species. Cats have been the cause of several large-scale exposures of humans to potentially rabid animals, including one situation involving over 600 PEPs (Noah et al., 1996; Rotz et al., 1998).

In a study assessing the risk of cat cases associated with different temporal stages of the raccoon rabies epizootics, there was a significant urban to rural trend in the increased risk of a cat testing positive for rabies. The risk of a cat testing positive for rabies [Odds Ratio (OR)] in rural counties in the lowest quartile for human population density (<61.6 inhabitants per mi^2) was 2.7-fold above the referent value (odds ratio = 1) for counties in the highest quartile of human population density (>420.2 inhabitants per mi^2); counties with intermediate human population densities, in the second and third quartiles, also showed increasing risk for cat rabies above counties with the highest human density, with odds ratios of 1.7 and 2.0 above the referent value, respectively (Gordon et al., 2004; Noah et al., 1996).

In Western Europe, where red fox rabies is the dominant form of endemic rabies and domestic dog rabies has long been controlled, rabies cases in cats remain a public health problem. Feral cat colonies are recognized as a potential hotspot for spillover of wildlife variants to cats; 14 rabid cats and no rabid dogs occurred between 1979 and 2000 (Mutinelli, 2010; Mutinelli, Stankov, Hristovski, Theoharakou, & Vodopija, 2004; Noah et al., 1996). Between 1979 and 2000, France reported rabies among 1,256 cats and 694 dogs, and between 1966 and 2000, Belgium reported 295 rabid cats and 64 rabid dogs (Aubert et al., 2004).

11.2 Rabies Virus Spillover to Livestock

Although not reservoirs for rabies virus, livestock species are susceptible to infection by variants maintained in other species. These species frequently are not vaccinated against rabies. At least one human death has been documented as a result of contact with a rabid domestic herbivore in Brazil (Brito et al., 2011). Mass human exposures have occurred where animals in public settings developed rabies. For example, in 2004, exposure to a suspect rabid sheep at a Texas wildlife center with an animal petting area resulted in more than 650 people receiving PEP (Star Telegram, 2004; Blanton, Krebs, Hanlon, & Rupprecht, 2006). Further examples include a rabid goat at a New York county fair in 1996, a rabid Wyoming rodeo pony in 1995, and two rabid Massachusetts dairy cows in 1998 and 1996, which resulted in prophylaxis for 465, 12, and 89 people, respectively (Centers for Disease Control and Prevention, 1999; Chang et al., 2002; Compendium of animal rabies prevention and control, 2004). Despite considerations that the oral route of exposure is realtively inefficient for transmission of rabies and a dilution factor of milk from a rabid cow in a bulk tank pool from a herd, 80 of the 89 people exposed to these rabid dairy cows received postexposure prophylaxis due to the ingestion of raw milk. Pasteurization temperatures inactivate rabies virus, therefore drinking pasteurized milk from a rabid animal is not a rabies exposure. Because animal-to-animal transmission is uncommon in livestock, quarantine of the exposed animal may not be warranted (Compendium of Animal Rabies Prevention and Control, 2004).

In the United States, cattle rabies has declined in a similar manner to that of dog rabies (Figure 3.12); from 2001–2010, an average of 85 cattle were reported rabid. Spillover of red fox rabies to cattle in Western Europe has exceeded the levels of dog and cat rabies over the past several decades. Between 1977 and 2000, 6,047 cases of cattle rabies were reported from Germany, 681 cases were reported from Austria (Muller, Cox, & Muller, 2004), and 5 cases were reported from Italy (Mutinelli et al., 2004). Between 1979 and 2000, 2,153 cases of cattle rabies were reported from France, and between 1966 and 2000, 1,629 cases of cattle rabies were reported from Belgium (Aubert et al., 2004).

12 EPIDEMIOLOGY OF MONGOOSE-ASSOCIATED RABIES

Dog-associated variants of rabies virus have been implicated in novel maintenance cycles in wildlife. For example, rabies in the Caribbean in the Asian yellow mongoose (*Herpestes javanicus*; formerly designated
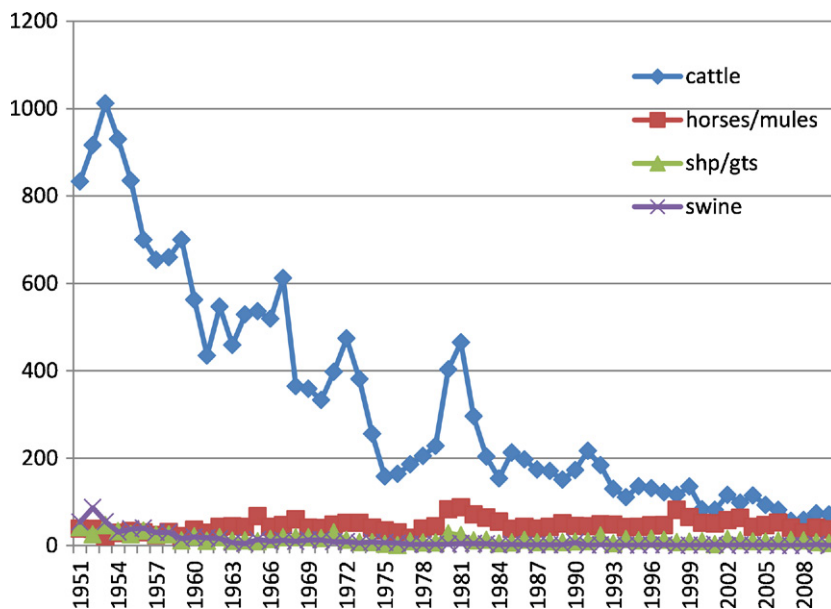
FIGURE 3.12 **Rabies diagnosed in selected species of livestock in the USA, 1951–2010, demonstrating the decline in rabid cattle as canine rabies was eliminated.**

as *Cynicus penicillata*; family *Herpestidae*) has been historically linked to when this species was introduced from Asia. Inter-island variation among the dog-associated rabies virus variants found in the mongooses is substantial and suggests multiple cross-species introductions of virus from dogs (Smith et al., 1992).

All mongooses present today in the Caribbean are descendants of animals brought from India to Jamaica in the 1870s for rodent control on sugar cane plantations (Everard & Everard, 1992). Although it is possible that rabies virus was introduced with these animals, official reports of rabies in mongooses in the Caribbean were not made until 1950 in Puerto Rico (Tierkel, Arbona, Rivera, & De Juan, 1952). Mongooses continue to be a source of human rabies in the Caribbean, where the virus is referred to as the dog/mongoose variant of rabies virus (Messenger et al., 2002).

In sub-Saharan Africa, rabies in the yellow mongoose (*C. penicillata*) appears to involve rabies virus variants distinct from those associated with domestic dogs. Data generated from recent molecular epidemiologic studies indicate an extended history of evolutionary adaptation of rabies virus within yellow mongoose and slender mongoose (*Galerella sanguinea*) populations in South Africa and Zimbabwe, respectively, and suggest that the enzootic area affected by these variants has a larger geographic range than previously suspected (Messenger et al., 2002; Nel et al., 2005).

13 CANINE RABIES VIRUS VARIANTS

Rabies virus variants associated with dog-to-dog transmission throughout the world demonstrate limited antigenic and genetic diversity (Nadin-Davis & Bingham, 2004; Smith, 1989). From these observations, it appears that dog rabies was probably introduced into South America, Africa, and parts of Asia due to translocation of dogs by early European colonialists. The similarity of canine rabies isolates from Latin America, Africa, Asia, and Eastern Europe reflect a global reservoir of rabies in dogs that arose from a common source. The isolate has been termed "the cosmopolitan strain" (Nel & Rupprecht, 2007). The cosmopolitan strain of rabies is believed to have its origins in the Paleartic region that includes Europe, the Middle East, and northern Africa (Nadin-Davis & Bingham, 2004; Badrane & Tordo, 2001). Nonetheless, there remains sufficient sequence variation among variants of rabies solely associated with dogs to detect differences within canine populations. This diversity permits epidemiological tracking of the dispersal of dogs, along with their human hosts, and directly influences patterns of rabies in countries such as Thailand (Denduangboripant et al., 2005).

Although significant numbers of feral, stray, or neighborhood dogs may contribute to free-ranging populations, human behaviors with regard to recruitment of companion animals, in addition to their interactions with stray or neighborhood dogs (Beck, 2000), can rapidly alter the demographic features of free-ranging dog populations.

Quantitative estimates of human mortality due to rabies have been frequently based on dog-bite injuries, estimates of the densities of dog populations, human population density and human-to-dog ratios, and knowledge of the incidence of bite injuries and risk of canine rabies within different populations of dogs (Brooks, 1990; Cleaveland et al., 2002; Cleaveland et al., 2003; Fevre et al., 2005; Knobel et al., 2005; Perry, 1993; Robinson, Miranda, Miranda, & Childs, 1996). The close relationship between reports of rabid dogs and human rabies deaths within countries where the cosmopolitan variant of rabies virus circulates within canines has been demonstrated in Africa, Asia, and South America and was widely appreciated within developed countries prior to canine rabies control (Belotto et al., 2005; Bingham, 2005; Denduangboripant et al., 2005; Tierkel, Graves, Tuggle, & Wadley, 1950).

Although variants of rabies virus introduced by domestic dogs have been implicated as the recent source of rabies virus independently circulating among several populations of wild carnivores, dogs remain the primary rabies threat for humans and animals in Africa (Talbi et al., 2009; Talbi et al., 2010). Similar to the situation in Zimbabwe, rabies virus variants believed to be circulating independently among a gray fox

(*U. cinereoargenteus*) reservoir in Colombia are most closely related to, and group phylogenetically with, domestic dog variants (Paez et al., 2005).

13.1 Management of Canine Rabies

The canine rabies virus variants responsible of dog-to-dog transmission of rabies can be pushed to extinction locally and regionally through comprehensive programs of parenteral vaccination and animal management. Canine rabies control through vaccination, reproduction control, movement restrictions, and habitat modification not only reduces the incidence of human rabies but also provides a cost-effective intervention for reducing the need of human PEP (Bogel & Meslin, 1990). Removal or culling of free-ranging dogs is not recommended as a primary means of dog population reduction or even as a supplementary measure to mass vaccination of dog populations (World Health Organization, 2005). The World Health Organization endorses national legislation in countries where such a program is affordable and enforceable (World Health Organization, 2005)

Mass vaccination campaigns in Africa indicate that a sufficiently high percentage of vaccine coverage can be achieved by the parental route in some urban settings (Kayali et al., 2003; Kayali, Mindekem, Hutton, Ndoutamia, & Zinsstag, 2006). Vaccination rates of 70% among free ranging dog (stray, feral, and neighborhood dogs) populations has been a traditional target promoted as sufficient to establish herd immunity (World Health Organization, 2005). However, theoretical estimates suggest herd immunity levels between 39 and 57%, with an upper 95% confidence interval of 55 and 71%, respectively, may prove sufficient to end epizootic transmission (Coleman & Dye, 1996; Kayali et al., 2006; Kayali et al., 2003).

13.2 The Risk of Pet Travel and Threat to Canine Rabies Prevention

The regulation and control of dog movements within and between countries remains an important strategy for preventing rabies. Rabies-free locations within a country, such as Hawaii in the United States (Fishbein, Corboy, & Sasaki, 1990) and rabies-free nations, such as the UK (rabies-free since 1922) and Japan, had traditionally enforced strict laws requiring 6 months of quarantine (Fishbein et al., 1990). The recent translocation of dogs with canine rabies virus variants into Europe and mainland USA demonstrates the very real risk for reintroduction of canine rabies virus variants into areas where they no longer exist (Castrodale, Westcott, Dobson, & Rupprecht, 2008; Johnson, Freuling, Horton, Muller, & Fooks, 2011).

The United Kingdom (UK) had initiated a Pet Travel Scheme (PETS) requiring imported animals to have an implanted microchip identification tag and documented proof of current vaccination, as evidenced not only by certificate documentation but also by the presence of antibody, within a six-month period prior to presenting proof of procedure at an official UK port (Jones, Kelly, Fooks, & Wooldridge, 2005). Several risk assessments models have been formulated in an attempt to estimate the probability through travel of pet animals of rabies introduction into the UK, which is currently free of terrestrial animal rabies. Having required either a 6-month quarantine for pet animals or evidence of seroconversion following rabies vaccination, the European Food Safety Authority (EFSA) in 2002 and the UK Veterinary Laboratories Agency (VLA) in 2011 specifically attempted to assess the consequence of abandoning the serological test to measure response to rabies vaccination in pet animals (DEFRA, 2011; Goddard et al., 2010; Scientific Committee on Animal Health and Animal Welfare, 2006). The EFSA concluded that serological testing is only beneficial when the waiting time after rabies vaccination exceeds 100 days. In other words, the value of serology would be in detecting low or non-responding animals whose titers may have initially been adequate but which subsequently declined in the interim or "waiting" period. There is also an implicit assumption that, while the animal intended for travel is in the "waiting" period, it should be held in a manner to preclude an exposure to rabies at its home location; for this recommendation to minimize risk, the confinement or quarantine conditions should be clearly stated. In contrast, the VLA concluded that the annual risk of rabies entry into the UK would increase tenfold if the serological test requirement was removed entirely, irrespective of any waiting period after vaccination. It is interesting to note that the model prediction of the number of years before rabies entry is quite long. Specifically, with current practices it is estimated as 13,272 years but declined to 1,152 years without serologic testing. The model identified that removing the serological test and reducing the waiting period to 30 days after vaccination would increase the annual risk of rabies entry such that the estimated number of years between entries was 322 years. Modeling is a powerful tool, but it is inherently limited by the data and design upon which the models are constructed. The power of modeling often comes from iterative refinement. Overall, the risk of rabies entry into the UK is significantly influenced by the inclusion of serologic testing. Moreover, what these models do not consider is that presenting a certificate of vaccination with an appropriately identified animal assumes the authenticity of the document with very little ability to verify this assumption through contact with the responsible veterinary practitioner.

To what level of scrutiny is the information on a rabies certificate form (http://www.nasphv.org/Documents/RabiesVacCert.pdf) held when

an animal is presented for travel, and how informative is this information? A measure of rabies immunity through a serum sample tested at a laboratory that is held to quality control practices and performance standard provides a somewhat higher degree of certainty about an animal's response to vaccination. Of course, deception could occur through this system by substitution of a blood sample from a different animal, but this would require collusion between an owner and veterinary practitioner. However, problems occur even with requirements for an official result from a qualified laboratory. Over the past three years, the Kansas State University Rabies Laboratory has documented approximately 75 instances of falsified rabies serology result documents that have been made to appear as if issued by our laboratory, but there is no record of such testing, during which time we tested over 100,000 samples by the fluorescent antibody virus neutralization method for pet travel (Hanlon, unpublished data). At present, regulatory authorities with jurisdiction over animal travel have Internet access to results from our laboratory so that they may verify whether a particular sample was tested at our laboratory. A critical component of prevention of disease translocation is education of owners and the public as to the importance of these requirements for disease prevention.

14 CONCLUSIONS

It is of paramount importance to keep in mind that the first essentials in reducing the risk and consequential damage of any type of disease introduction or novel emergence are to maintain diagnostic capabilities at specialty labs and to assess threats posed by outbreaks in other countries. Potential emergent "hotspots" (Keesing, Belden et al., 2010) that may be identified based on land-use change and biodiversity patterns should be targeted for surveillance of endemic rabies virus variants, and other viruses, that may have the potential to jump host species. Lastly, wherever possible, adequate disease surveillance measures aimed at intensively farmed livestock in newly developed clearings juxtaposed to intact natural habitats and in locations, such as wetmarkets, where wild caught animals are held in close-proximity to domesticated species, could provide early warnings of outbreaks such as Nipah virus and SARS coronavirus (Chua, Goh et al., 1999; Drosten, Gunther et al., 2003). However, managing potential emergence hotspots by attempting to alter the ecology of high-risk areas is likely to be detrimental because the species most resilient to habitat destruction and degradation may be those that amplify pathogen transmission.

Like many zoonoses and other emerging infections, rabies prevention requires the cooperation of animal control, law enforcement, natural

resource personnel, veterinarians, diagnosticians, public health professionals, physicians, and others. The risk of disease translocation can be mitigated through carefully crafted requirements for animal identification, vaccination, serological monitoring, and advance planning essentially equivalent to a quarantine period. A critical component is education of owners and the public as to the importance of requirements. Historically, rabies diagnosis and prevention has been a core part of public health practice at local and state health agencies. With declining case numbers and substantial pressure from economic constraints, a number of public health laboratories are moving away from rabies diagnosis. The Kansas State University Rabies Laboratory provides rabies diagnostic testing and virus characterization on positive samples for a number of states and localities because it is within the public health mission of this educational, nonprofit, state university laboratory.

Much of the public remains insulated and largely unaware of rabies transmission patterns either locally or globally. The unpredictability of human behavior and lack of awareness of the hazards of not complying with reasonable regulations present the greatest threat of disease translocation and associated exposures and potential mortality. Although rabies excites the imagination, current vulnerabilities include the potential for reintroduction of dog-to-dog transmitted rabies, a decline in diagnostic expertise and capacity, and a lack of basic research, especially to understand recent advances, or lack thereof, towards treatment of clinical rabies. As we increasingly approach the reality of global community with rapid and high volume exchange of animate beings, diligent attention and dedicated effort will be required to maintain and indeed, even advance emerging and zoonotic disease control, with rabies as a tangible "best-practices" template, beyond the major advances made in the last 50 years.

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