

Emerging Epidemiology of Bat-Associated Cryptic Cases of Rabies in Humans in the United States

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In the United States, during the past half-century, the number of humans to die of rabies dramatically decreased to an average of 1–2 per year. Although the number of deaths is low, most deaths occur because individuals are unaware that they had been exposed to and infected with rabies virus, and, therefore, they do not seek effective postexposure treatment. Molecular epidemiological studies have linked most of these cryptic rabies exposures to rabies virus variants associated with insectivorous bats. In particular, virus variants associated with 2 relatively reclusive species, the silver-haired bat (*Lasionycteris noctivagans*) and the eastern pipistrelle (*Pipistrellus subflavus*), are the unexpected culprits of most cryptic cases of rabies in humans.

In the United States, the number of cases of rabies in humans, particularly those resulting from domestic exposures (i.e., indigenous cases), has decreased precipitously since the early 20th century. The few cases remaining, however, present particularly difficult challenges for both public health and medical communities. In contrast to the vivid imagery of attacks by mad dogs recounted in historical writings and art since at least the 23rd century B.C. [1], most recent indigenous cases of rabies (63% of 70 cases in 1958–2001, including 89% of 28 cases since 1980) involved no documented evidence of a bite from a rabid animal. Human deaths due to cryptic rabies have become the rule in the United States.

Cryptic rabies cases are those in which a clear history of exposure to rabies virus cannot be documented, despite extensive case-history investigation. Absence of a documented bite history reflects inherent difficulties in obtaining accurate animal-contact information, particularly when the patient is incoherent, in a coma, or has died. In such cases, one must rely on interviews with family, friends, and acquaintances for evi-

dence of animal contact [2, 3]. Thus, absence of bite-history data does not mean that a bite did not occur. Long incubation periods, which are documented in some cases, could hinder recollection of a bite [3–6], or bites may be overlooked, particularly if the vector is small (e.g., some bat species) [7]. For example, Feder et al. [8] described a woman who reported that a bat “brushed against her,” but that she did not perceive a bite or scratch. Bite marks were only evident with the aid of an otoscope that revealed 2 pinpoint puncture wounds. Moreover, bites from bats or nonreservoir species (e.g., domestic cats) may not be evaluated properly as posing a risk for rabies virus transmission. Finally, rabies virus can be transmitted without a bite or scratch if the virus comes into contact with a breach in the skin or with intact mucous membranes.

One implication of cryptic exposure is that the rabies reservoir species responsible cannot be easily identified, hindering public health personnel in their effort to recommend preventative measures. In addition, when rabies is not suspected until well after the onset of clinical signs and symptoms (possibly not until after death), greater numbers of health care workers, family members, and friends are at risk of being exposed to it [2, 9]. In 1980–1996, the median number of persons requiring costly postexposure treatment per rabies case in humans was 54 [10]. In a worst-case scenario, rabies virus has been transmitted from persons with undiagnosed cases to other individuals through organ transplantation (i.e., cornea transplantation) [11]. There is also the possibility that rabies is underdiagnosed in the United States [9].

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EPIDEMIOLOGY OF BAT RABIES AND THE ROLE OF BATS IN CRYPTIC EXPOSURE IN THE UNITED STATES

Monoclonal antibodies specific to rabies viral proteins provided the first hint that insectivorous bats may be involved in human deaths caused by cryptic rabies (table 1). Although insectivorous bat rabies was not recognized in the United States until 1953 [12], genetic evidence suggests that rabies is an old disease for bats in the New World (Old World bat species have been found infected with lyssaviruses other than rabies virus) [9]. Individual bats from most of the estimated 41 bat species in the United States [13], when sampled in sufficient numbers, have been found to be infected with rabies virus [14, 15]. In addition, by use of monoclonal antibody panels, rabies viruses recovered from bats were shown to be distinct from rabies viruses recovered from terrestrial mammals, suggesting that these viruses evolved within their bat hosts [15–20].

More discriminating molecular typing (i.e., RT-PCR and sequencing) revealed that bat rabies viruses were genetically diverse, exhibiting mutations characteristic to each host bat species [21–24]. These data suggest that rabies viruses are maintained in animal populations predominantly through intraspecific transmission. That is, transmission rarely occurs between species, such as when a rabid bat infects a human. These “spillover events” generally are not perpetuated in the recipient species. Less frequently, rabies viruses jump species boundaries and acquire new host species that then contribute to long-term maintenance of rabies. Because rabies viruses sampled from different reservoir species are genetically distinct, patterns of virus transmission within and between species can be monitored.

Molecular typing of rabies viruses isolated from patients revealed that, of 35 indigenous rabies cases in the United States analyzed during 1958–2000, rabies viruses associated with insectivorous bats accounted for 32, including cases in 26 of 28 patients with no bite history (figure 1; author’s unpublished data) [21–23]. Unexpectedly, 19 of 26 bat-associated cryptic cases were attributed to rabies viruses not from common house bat species, but, rather, from 2 bat species rarely found around humans or human dwellings: silver-haired bats (*Lasiurus noctivagus*) and eastern pipistrelles (*Pipistrellus subflavus*). Of interest, the first well-documented human death due to rabies associated with an insectivorous bat bite (in 1958) was also the first case reported to involve silver-haired bats in human rabies [25, 26]. The species was identified because the bite was recognized and the bat was recovered. Subsequent cases involving silver-haired bat viruses were documented only by molecular typing of rabies viruses isolated from patients.

Silver-haired bat rabies viruses also have been detected frequently in eastern pipistrelles, leading researchers to question whether eastern pipistrelles represented an independent res-

ervoir. Only recently has increased sampling of rabid silver-haired bats and eastern pipistrelles over a broader geographic region provided the necessary evidence to indicate that eastern pipistrelles are a second rabies reservoir species that is independent of silver-haired bats. Moreover, rabies viruses from eastern pipistrelles have accounted for more human deaths ($n = 16$) than have viruses from silver-haired bats ($n = 8$).

Although molecular typing has proven invaluable for identifying reservoir species for rabies viruses implicated in human deaths, the identity of the species delivering the bite (i.e., vector species) might be different (e.g., spillover) and is contingent on additional case-history data (e.g., history of animal bite or contact). For example, in 3 of 26 bat-associated cryptic case investigations, epidemiologists documented contact with a sick domestic animal, raising the possibility that, although bat species were the reservoirs of the implicated viruses, other species (which were infected with those bat viruses) may have delivered the fatal bites. Studies that have evaluated the prevalence of bat rabies variants among domesticated animals, however, have suggested that such spillover is rare and that it is unlikely to account for most cases in humans [17–18, 27]. Moreover, in 16 of the bat-associated cryptic cases, either bats in the home ($n = 4$) or physical contact with bats ($n = 12$) was identified, suggesting that bats were likely the source of unnoticed bites in these cases. Because bats were not collected in most cases, however, it is unclear which species accounted for the bites.

Finally, another piece of evidence—although circumstantial—suggesting that insectivorous bats are the source of cryptic exposures is that contact with bats predominantly occurs during the late summer months (figure 2A); if contact leads to infection, onset of symptoms occurs an average of 4–8 weeks later. Exposure to and onset of rabies symptoms from exposure to other terrestrial viruses is less seasonal. Onset of most cases of bat-associated cryptic rabies cases in humans occurred in the fall, which is consistent with exposure to bats during the late summer (figure 2B). Although these data are compelling, there clearly is a gap in our knowledge of the role of bats in cryptic rabies cases in humans, which makes it hard to draw conclusions. It is particularly difficult to explain why most rabies-related deaths in humans are associated with rabies viruses (i.e., those associated with *L. noctivagus* and *P. subflavus* variants [Ln/Ps variants]) that otherwise appear to be rarely encountered.

PREVALENCE OF THE LN/PS VARIANTS AND THE INFLUENCE OF SEASONAL DISTRIBUTION AND MIGRATION

One plausible explanation for the preponderance of rabies cases in humans that are associated with Ln/Ps variants is that these rabies variants are more widespread than has previously been

Table 1. Summary of cases of rabies in humans in the United States included in the study.

Patient	State	Year	Case history investigation and summary	Diagnosis of reservoir ^a	
				Case history	Molecular data
1	California	1958	Bitten by rabid silver-haired bat; received ineffective PEP	Bat	Bat (Ln)
2	Texas	1961	Bitten by dog in Mexico	Dog	Dog (Mexico)
3	Oregon	1967	Bitten by neighbor's dog in Egypt; received ineffective PEP	Dog	Dog (Old World)
4	Texas	1972	Bitten by dog in The Philippines	Dog	Dog (The Philippines)
5	Kentucky	1973	Bitten by bat while sleeping at home in Kentucky	Bat	Bat (Ps)
6	Minnesota	1975	Bitten by stray cat at home in Minnesota; received ineffective PEP	Unknown	Skunk (north central United States)
7	California	1975	Bitten by dog in Coatzengo, Puebla, Mexico	Dog	Dog (west Mexico/United States)
8	Maryland	1976	Bitten by bat outdoors at home in Maryland; received ineffective PEP	Bat	Bat (Ps)
9	Texas	1976	Bitten by dog in Monclova, Coahuila, Mexico	Dog	Dog (northeast Mexico/United States)
10	Indiana	1978	Received corneal transplant; virus detected in cornea postmortem; no known animal bite exposure	Unknown	Bat (Ln)
11	Texas	1979	Bitten by dog in Piedras Negras, Coahuila, Mexico	Dog	Dog (northeast Mexico/United States)
12	Texas	1979	Bitten by dog in Coahuila, Mexico; received ineffective PEP	Dog	Dog (northeast Mexico/United States)
13	California	1979	Bitten by dog in Parral, Chihuahua, Mexico	Dog	Dog (west Mexico/United States)
14	Oklahoma	1979	No known animal bite exposure	Unknown	Bat (Ps)
15	Kentucky	1979	No known animal bite exposure	Unknown	Bat (Ps)
16	Oklahoma	1981	No known animal bite exposure	Unknown	Skunk (south central United States)
17	Arizona	1981	Bitten by dog in Guaymas, Sonora, Mexico	Dog	Dog (west Mexico/United States)
18	Massachusetts	1983	Bitten by dog in Nigeria	Dog	Dog (Nigeria)
19	Michigan	1983	Child reported account of bat bite; parents found no bat or evidence of bite	Bat	Bat (Ln)
20	Texas	1984	Bitten by dog in Laos, but dog remained healthy	Unknown	Dog (Southeast Asia)
21	Pennsylvania	1984	Bitten by healthy cat 6 days before onset of symptoms; cat later disappeared	Unknown	Bat (Mc)
22	California	1984	Bitten by dog in Montufa, Guatemala	Dog	Dog (Mexico/Guatemala)
23 ^b	Texas	1985	No known animal bite exposure	Unknown	Dog (Mexico City)
24	California	1987	Bitten by dog in The Philippines, but dog remained healthy	Unknown	Dog (The Philippines)
25	Oregon	1989	No known animal bite exposure	Unknown	Dog (Mexico City)
26	Texas	1990	Bitten while handling a bat inside a building in Texas	Bat	Bat (Tb)
27	Texas	1991	Bitten by dog 46 years earlier in Mexico; no other known animal bite exposure	Unknown	Dog/coyote (northeast Mexico/United States)
28	Arizona	1991	Contact with bat in house	Unknown	Bat (Ps)
29	Georgia	1991	No known animal bite exposure	Unknown	Bat (Ps)
30	California	1992	Bitten by dog in India	Dog	Dog (India)
31 ^b	New York	1993	Contact with captive bat in house; conflicting accounts of whether bat was released or discarded or whether it died; no known animal bite exposure	Unknown	Bat (Ps)
32	Texas	1993	Contact with sick cow that died of unknown disease; no known animal bite exposure	Unknown	Bat (Ps)
33	California	1993	Bitten by dog in Ecatepec, Mexico (near Mexico City)	Dog	Dog (Mexico City)
34	California	1994	Contact with sick stray cat that disappeared; no known animal bite exposure	Unknown	Bat (Ln)
35 ^b	Florida	1994	No known animal bite exposure	Unknown	Dog (Haiti)

(continued)

Table 1. (Continued.)

Patient	State	Year	Case history investigation and summary	Diagnosis of reservoir ^a	
				Case history	Molecular data
36 ^b	Alabama	1994	Contact with dead bats removed from old home; rabies-positive bats later collected from home; no known animal bite exposure	Unknown	Bat (Tb)
37	West Virginia	1994	Potential contact with moribund or dead bat	Unknown	Bat (Ps)
38	Tennessee	1994	Potential contact: history of bats in residence; no known animal bite exposure	Unknown	Bat (Ps)
39	Texas	1994	Contact with sick puppy; no known animal bite exposure	Unknown	Dog/coyote (northeast Mexico/United States)
40	Washington	1995	Potential contact: rabid <i>Myotis</i> bat found in bedroom where child was sleeping; no known animal bite exposure	Unknown	Bat (Mc)
41	California	1995	Contact with bat that landed on chest at work in California; no known animal bite exposure; colony of bats roosting in open rafters of packing shed, but none of 76 in colony were positive for rabies	Unknown	Bat (Tb)
42	Connecticut	1995	Potential contact: siblings reported flying bat, bird, or moth in room where child was sleeping; no known animal bite exposure	Unknown	Bat (Ps)
43 ^b	California	1995	Contact with bats; history of catching bats; no known animal bite exposure	Unknown	Bat (Ln)
44	Florida	1996	Bitten by dog in Chiapas, Mexico	Dog	Dog (Mexico/Guatemala)
45	New Hampshire	1996	Bitten by dog in Nepal	Dog	Dog (Nepal)
46 ^b	Kentucky	1996	No known animal bite exposure	Unknown	Bat (Ps)
47	Montana	1996	No known animal bite exposure	Unknown	Bat (Ln)
48 ^b	Montana	1997	Contact with bats captured and removed from home; no known animal bite exposure	Unknown	Bat (Ln)
49	Washington	1997	Contact (sting/bite from unidentified source); no other known animal bite exposure	Unknown	Bat (Ef)
50	Texas	1997	Contact with bat that landed on shoulder while sleeping in motel in Texas; no bite wound evident	Unknown	Bat (Ps)
51	New Jersey	1997	Contact with bats captured and removed from home; no known animal bite exposure	Unknown	Bat (Ps)
52	Virginia	1998	No known animal bite exposure	Unknown	Bat (Ps)
53	California	2000	Contact with a bat removed from home; no known animal bite exposure	Unknown	Bat (Tb)
54	New York	2000	Bitten by puppy in Ghana	Dog	Dog (Africa)
55	Georgia	2000	Contact with bats landing on him while sleeping in home; no known animal bite exposure	Unknown	Bat (Tb)
56	Minnesota	2000	Bitten by bat in home; did not seek PEP	Bat	Bat (Ln)
57 ^b	Wisconsin	2000	Contact with bats removed from home; no known animal bite exposure	Unknown	Bat (Ps)

NOTE. Ef, *Eptesicus fuscus*; Ln, *Lasionycteris noctivagans*; Mc, *Myotis californicus*; PEP, postexposure prophylaxis; Ps, *Pipistrellus subflavus*; Tb, *Tadarida brasiliensis*.

^a Cases listed as unknown in "Diagnosis of reservoir" but describing bites in "Case history investigation" indicate a bite by a nonreservoir species (e.g., cat) or a bite by an animal not considered to be the cause of the rabies infection (e.g., incubation time too long or too short or animal remained healthy).

^b DNA extracted from patients were from formalin-fixed tissues.

recognized. Surveillance studies performed by state health departments, however, reject that either the bat species or the rabies variants are common. The prevalence of rabies in bat populations in the United States is estimated to be <1% among bats sampled randomly from natural populations and 3%–25% among bats submitted to state health departments [15, 28–33]. With few exceptions, neither silver-haired bats nor eastern pipistrelles constituted >5% of all bats submitted to state health

departments, and the prevalence of rabies in these 2 species is generally <5% of bat viruses typed [22, 29, 31, 34–36]. Although the Ln/Ps variants have been detected in other species, molecular epidemiologic studies found that spillover to other bats (author's unpublished data) [9] or terrestrial mammals [15–16, 24, 37] rarely occurs. For example, *Eptesicus fuscus* constitute a large proportion of bats that have rabies diagnosed in the United States, yet only 2 of 117 rabid *E. fuscus* bats surveyed

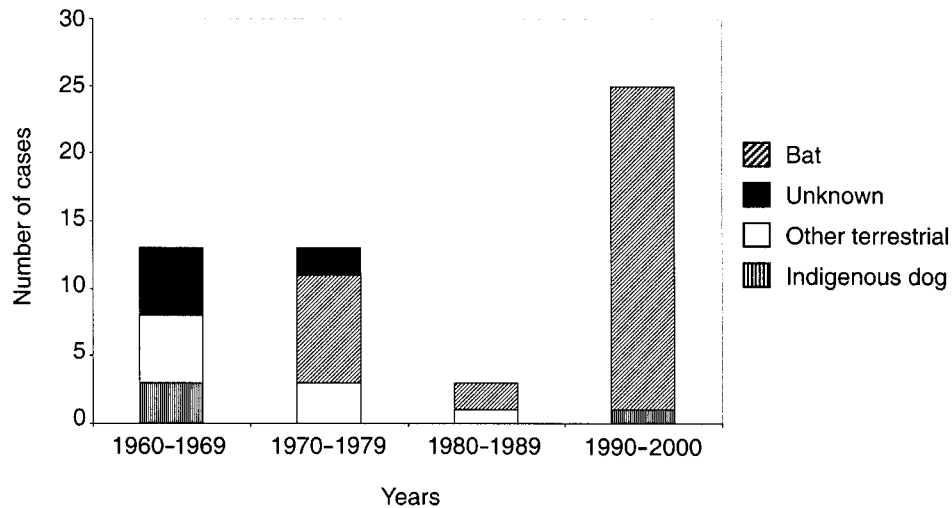


Figure 1. Number of human rabies deaths in the United States (1960–2000) attributed to viruses from indigenous domestic dogs, other terrestrial mammals, bats, or unknown sources. Data compiled from *Morbidity and Mortality Weekly Report* data documenting rabies cases in humans in the United States.

were infected with the Ln or Ps variants [38]. *Myotis lucifugus* also is submitted in large numbers for rabies diagnosis, but it is rarely found to be rabid (16 of 2204 *M. lucifugus* bats were found to be rabid [31]). This suggests that *M. lucifugus* is not a reservoir for any rabies virus.

Although surveillance data do not support the notion that the Ln/Ps variants are common, these variants might be locally common in regions where cases in humans occur. Silver-haired bats are migratory, solitary, and reclusive tree-dwelling bats patchily distributed throughout the United States (except Hawaii and possibly Florida) and southern Canada [39], yet rabies cases in humans associated with this bat virus occur only in the northwestern and north-central regions of the country (figure 3). This may be explained in part by the fact that this species is locally abundant in northern regions (particularly in the northern Rocky Mountains) [36, 39, 40] during the summer when most exposures to rabid bats occur (figure 2). In addition, in a 5-year study (1971–1975) of silver-haired bats, Dorward et al. [41] found that the highest incidence of rabies in this species in Canada was during August and September. Other researchers have noted that the incidence of rabies-infected bats peaks in August [29, 36, 42]. Young bats that are born in this northern region may provide a pool of new susceptible bats important for long-term maintenance of rabies in the species [29] and may be responsible for many human exposures in that region. Young rabid bats would likely not survive the southerly migration, which accounts for the absence of rabies cases in humans further south. Interestingly, Dorward et al. [41] found that >84% of rabid bats (of several species) tested in Alberta were young bats born that year.

Cases of rabies in humans that are associated with the Ps variant are widely spread throughout the eastern US distri-

bution of eastern pipistrelles (figure 3). Eastern pipistrelles are relatively sedentary, moving short distances between summer roosts and hibernacula (generally caves). Because eastern pipistrelles prefer sheltered caves during winter hibernation, their distribution is also patchy and tends to be greater in regions with suitable cave systems. Much more data are needed to determine whether local population densities of eastern pipistrelles are greater where human cases have occurred. Of interest, in states where human cases associated with the Ps variant occurred, the state health departments' submission records suggest that eastern pipistrelles are rarely encountered, whereas, in Indiana (the state in which the highest prevalence of eastern pipistrelles was recorded), no cases of rabies occurred in humans. Additional study is necessary to determine whether the prevalence of silver-haired bats and eastern pipistrelles has been underestimated, either seasonally or in localized geographic regions where human cases occur. To date, however, no data indicate that the Ln/Ps variants are common.

PATHOGENESIS OF RABIES VIRUSES ASSOCIATED WITH SILVER-HAIRED BATS AND EASTERN PIPISTRELLES

Recent studies have proposed the intriguing hypothesis that the Ln/Ps variants have evolved genetic changes that may allow a higher likelihood of infection after superficial contact [43, 44]. A series of experiments comparing the pathogenicity, cell tropism, and chemical and antigenic properties of viruses isolated from silver-haired bats, domestic dogs, and coyotes found that, although all rabies virus variants grew to equal titers in nerve tissue, rabies viruses isolated from silver-haired bats grew to higher titers in epithelial and muscle tissue. They also noted

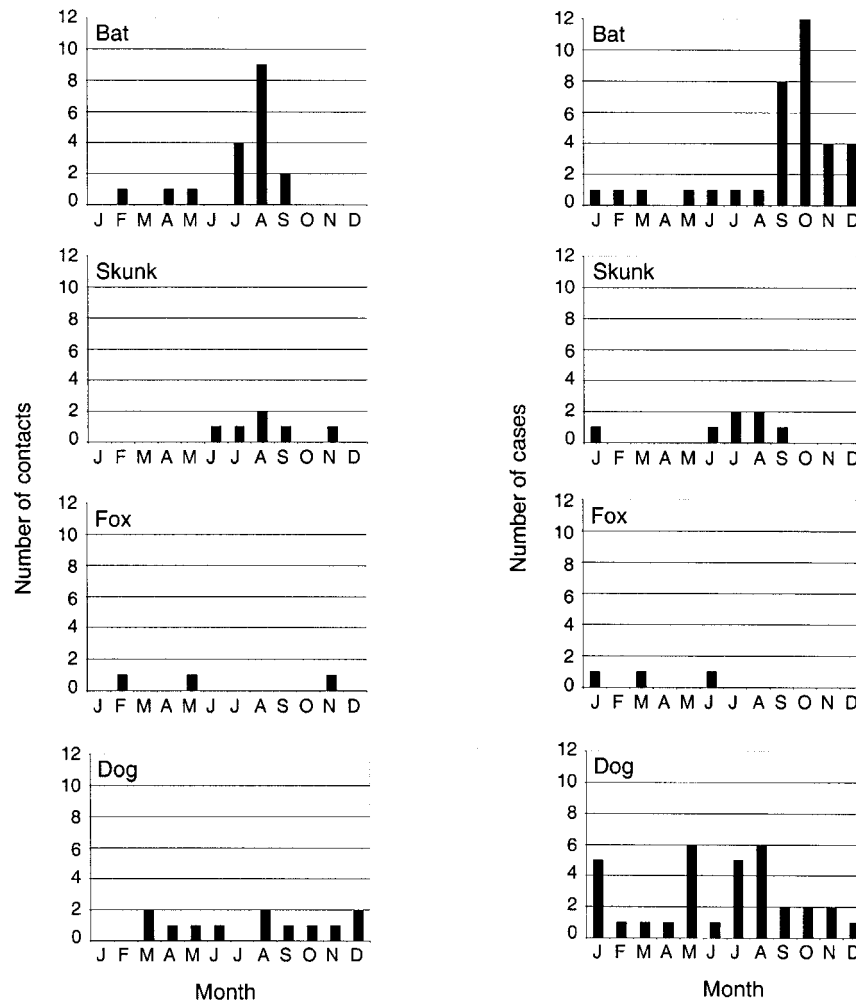


Figure 2. Human rabies reservoir contacts (*left*) and onset of human rabies cases (*right*), by month and rabies virus variant. Data compiled from US Public Health Reports (1957–1959) and *Morbidity and Mortality Weekly Report* data documenting US human rabies cases (1960–2000).

that these results were more marked at lower temperatures (34°C). In addition, they discovered molecular changes in the structure of the glycoprotein, particularly in antigenic site IIIB, that might be linked to increased infectivity [43, 44].

In many cryptic exposures involving the Ln or Ps variants, presence of a bat in the home was documented, possibly leading to an unnoticed superficial bite by a bat. Although superficial exposure to a bat or other animal infected with almost any variant of rabies virus has a low risk of disease [45, 46], the experimental data suggest that the potential for lethal infection seems to be increased if the superficial exposure involves Ln/Ps variants. The experimental data are compelling; however, comparisons between the Ln/Ps variants and other bat viruses have not been made. Such comparisons are necessary to demonstrate that increased infectivity is unique to the Ln/Ps variants and thus possibly linked to their prevalence among humans who die of rabies. Further study of the infectivity and pathogenicity of all bat rabies viruses is warranted.

Despite the increased prevalence of Ln/Ps variants among humans who die of rabies, it is important to remember that, in these cases, disease is not the result of treatment failure but the result of a failure to seek treatment. Current vaccines are effective against all known variants of rabies virus, including the Ln/Ps variants [47, 48], but vaccines can prevent rabies infection only if a risk of disease transmission is recognized.

IMPACT OF CRYPTIC EXPOSURE ON RABIES DIAGNOSES

The complete recovery from rabies of a young boy in 1970 [49] offered the possibility that early diagnosis, intensive care, and antiviral therapy might lead to additional recoveries; however, the lack of any subsequent success (i.e., others have survived rabies, but they experienced severe sequelae) has dampened enthusiasm for experimental treatments for rabies. Antemortem diagnosis is now sought as a means to eliminate the expense and

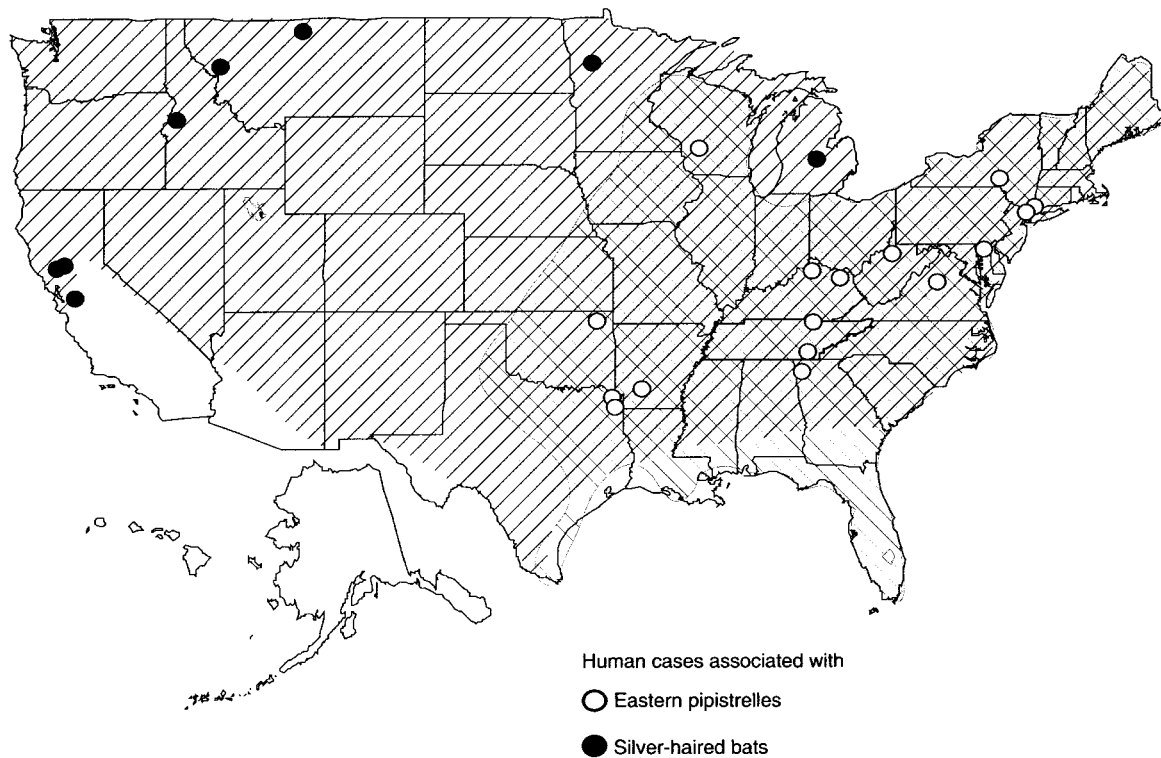


Figure 3. Rabies cases in humans in the United States associated with silver-haired bat (solid circle) and eastern pipistrelle (open circle) rabies virus variants. Hatchmarks sloping down to the right indicate the distribution of eastern pipistrelles (*Pipistrellus subflavus*); hatchmarks sloping down to the left outline the distribution of silver-haired bats (*Lasiurus noctivagus*); crossed hatchmarks indicate where both species co-occur.

discomfort of unnecessary diagnostic tests and medical treatment of the patient, to decrease the number of persons potentially exposed to rabies by contact with the patient, and to identify others possibly exposed to the same rabies vector.

Early diagnosis is critical to reducing expensive postexposure treatment. Anderson et al. [50] found that a greater average number of individuals required postexposure treatment when diagnosis was made >1 week after hospitalization ($n = 72$), compared with ≤ 1 week after hospitalization ($n = 20$). Rabies virus replicates to high titer in the CNS before development of systemic symptoms in the patient, and virus may be present in the brain for a week or more before signs of encephalitis are evident (reviewed in [45, 51]). Clinicians rarely suspect rabies in hospitalized patients earlier than 7 days after the onset of symptoms [10, 52]. By this time, infection has spread centrifugally from the brain. Virus, viral antigen, or viral RNA can be detected in peripheral nerves and tissues, and antibody is often present in both serum and CSF.

Two factors—definite or probable exposure history and presence of aerophobia or hydrophobia—were significantly associated with premortem diagnosis ($P < .05$) [50]. In cryptic rabies exposures, however, clinicians cannot rely on the reporting of an animal bite before suspecting rabies. Rather, increased scrutiny of any patient with acute, rapidly progressing enceph-

alitis is warranted [10]. In almost all rabies cases, the patient is hospitalized <1 week after onset of clinical signs and, where data are available, is comatose <1 week after signs of encephalitis appear. In addition, paresthesia, agitation, and paralysis are suggestive of rabies and may enable earlier detection of a case [10, 50]. In particular, paresthesias at the site of the bite wound are reported frequently (54 of 88 cases during 1957–2000) and often are among the first signs in the clinical syndrome. Of interest, 22 of 54 patients who exhibited paresthesias had no known bite history, again suggesting that bites occurred but were either not noticed or not reported.

Because of the implications of a positive rabies test result, a finding of rabies should be confirmed in >1 tissue or sample (table 2). The relative success of different diagnostic methods for different samples was recently reviewed [10, 52, 53]. Clinicians are encouraged to contact their state health departments for instructions on how to submit a complete set of samples for rabies diagnosis.

CRYPTIC RABIES AND THE QUESTION OF AEROSOL TRANSMISSION

The notion of cryptic rabies cases, particularly when associated with bats, raises the question of aerosol transmission of rabies

Table 2. Methods for diagnosis of cases of rabies in humans, 1991 to present.

Sample and diagnostic method ^a	No. of positive diagnoses/ total no. tested
Saliva	
RT-PCR	16/16
Virus isolation ^b	
Antibody negative	13/15
Antibody positive	0/17
Skin biopsy, FAT	15/20
Serum, serologic testing ^c	13/22
CSF	
Serologic testing	3/13
RT-PCR	0/4
Corneal epithelium, ^d FAT	3/9
Brain biopsy, ^e FAT	3/3

NOTE. FAT, fluorescence antibody test.

^a Nested PCR was required in almost all cases to compensate for the often extremely limited amount of RNA in some antemortem samples.

^b Virus isolation data suggest that detection may become more difficult as an immune (antibody) response develops to rabies infection.

^c Serologic tests (by rapid fluorescent focus inhibition test or indirect assay) found antibody in samples collected as early as day 5 of the clinical course, but antibody was absent as late as day 24 in 1 patient.

^d Corneal tissue is difficult to sample correctly, especially from comatose patients, and it should be obtained only by an ophthalmologist after consultation with the rabies-testing laboratory.

^e The rarity of human rabies and the lack of an effective treatment make routine brain biopsy unwarranted.

virus. Following on the heels of the first diagnosis of rabies in an insectivorous bat in 1953 [12, 54], 2 individuals died of rabies (in 1956 and 1959) after entering caves in which large colonies of Mexican free-tailed bats (*Tadarida brasiliensis*) roosted. Neither reported any evidence of bites by bats [55, 56]. Because of the concern that the human cases might have resulted from aerosolized transmission of rabies virus, researchers investigated the potential for aerosol transmission of rabies to caged animals (mostly canids) held in caves [57–59]. They concluded that aerosol transmission of rabies virus was possible, but only in a few US caves with very large bat colonies coupled with extreme humidity, high temperature, and poor ventilation. They also suggested that the high ammonia concentration and abundance of ectoparasites in these caves were a natural deterrent to human entry. No additional cases of rabies in humans have been attributed to exposure to bats in caves, and investigations of the 2 reported human cases revealed that both infections could be explained by means other than aerosol transmission (reviewed in [60]). Because the size of bat colonies in human dwellings is much smaller, and because the environmental conditions (e.g., ventilation and relative humidity) in attics and other bat roosting areas in houses and barns are not conducive to aerosolization of any excreted rabies virus, ex-

posure to the air around these smaller bat colonies is not considered to carry a risk of rabies.

RECOMMENDATIONS FOR POSTEXPOSURE PROPHYLAXIS

Cryptic rabies cases present a difficult challenge for physicians evaluating the need for postexposure prophylaxis. Current recommendations suggest that postexposure prophylaxis be considered even if a bite, scratch, or mucous membrane exposure is not apparent if it is possible that such an exposure occurred [47, 61–63]. Inappropriate administration of postexposure prophylaxis is also a concern because of the cost and limited supplies of reagents (e.g., human rabies immunoglobulin, or HRIG) [64–67]. Thus, rational assessment of the need for postexposure prophylaxis may require more-detailed questioning of the patient on the nature of the possible exposure and risk of infection.

Prevention of exposure to rabies virus is critical to minimizing the number of rabies cases in humans. In light of the current epidemiologic patterns, increased education of the public is needed to encourage (1) avoidance of physical contact with wildlife, especially bats [68]; (2) exclusion of bat roosts in homes (humane methods are feasible); (3) vaccination of pets; (4) cognizance that even nonbite exposures to sick domestic animals pose a risk (any animal that dies after rapid onset of illness and decline in health should be considered for rabies testing) [34, 69, 70]; and (5) testing rather than release of any bat found in the home when an exposure cannot be ruled out.

The current recommendations are not without controversy [71], but, if they are adhered to rather than overinterpreted, they are sound and based on the best available knowledge. Questions remain unanswered on the natural history of bats (particularly silver-haired bats and eastern pipistrelles), bat-human interactions, as well as ecologic and evolutionary characteristics of disease in bat populations. More research in these areas is needed to improve our understanding of the risks to humans of rabies infections associated with bats.

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