

Mammalian Reservoirs and Epidemiology of Rabies Diagnosed in Human Beings in the United States, 1981–1998

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ABSTRACT: Between 1981 and 1998, 37 cases of rabies were diagnosed in human beings in the United States. Information directly linking the cause of infection to animal bite was available for only eight of these cases. Indirect incrimination of the vector by analysis of cDNA sequences obtained by reverse transcriptase polymerase chain reaction of samples indicated that for all cases (12/12) believed to have been acquired in foreign countries, variants of the rabies virus (VRVs) associated with dogs (7/12 involved known bite histories) were the cause of the rabies infections. In contrast, VRVs associated with bats (bat-associated VRVs or BAVs) were implicated as the cause of 88% (22/25) of infections believed to have been acquired within the United States (1/22 involved known bite histories). Sequence analyses revealed that a single BAV (Ln/Ps), associated with rabid silver-haired (*Lasionycteris noctivagans*) and Eastern pipistrelle (*Pipistrellus subflavus*) bats, was implicated in 73% (16/22) of bat-associated infections. Silver-haired bats are predominantly solitary and migratory. Eastern pipistrelle bats may occur individually or in small clusters. Both species are only infrequently submitted for rabies testing. Unrecognized bites and unique properties of the Ln/Ps BAV may explain its association with the majority of rabies infections in human beings in the United States.

INTRODUCTION

Rabies has been enzootic or epizootic in domestic or wild animals in the United States for much of the nineteenth and twentieth centuries. The greatest numbers of annual human deaths were recorded during the first half of this century, with an average of about 50 cases (range of 18 [1950] to 105 [1928]); most resulted from the bite of infected dogs (Centers for Disease Control and Prevention [CDC] records and Office of Vital Statistics Records).¹ Following the control of canine rabies in the 1940s and 1950s, the number of indigenously acquired human rabies cases fell to an average of about two per year during the 1960s and 1970s.²

In developing nations throughout much of the world, the domestic dog remains the animal most frequently reported rabid, but in the United States and many other

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industrialized nations, rabies today is primarily a disease of wildlife. Vaccination of domestic animals, ongoing education programs, and an efficient public health infrastructure remain effective strategies for the prevention of transmission of terrestrial rabies variants to human beings. In addition to these proven effective strategies, oral vaccination of wildlife via the use of vaccine-laden baits is a safe, and potentially effective approach to prevent transmission of terrestrial rabies.³⁻⁵ However, during the past decade, in the United States, a disproportionate and increasing number of cases of rabies in human beings has been the result of infection by variants of the rabies virus (VRVs) that are associated with bats (bat-associated VRVs or BAVs),⁶⁻⁹ a wildlife group difficult to target for control by conventional methods. Compounding the difficulties already inherent in preventing rabies transmission from non-terrestrial animals is the fact that the exposure history in almost every one of these human cases remains unknown or at least questionable.

BACKGROUND AND METHODS

During the past two decades, advances in immunology and molecular biology have provided the tools to allow a greater understanding of the enzootic patterns of maintenance and distribution of the rabies virus in naturally occurring populations. Within broad areas of the United States, circulation of rabies infections in terrestrial animals is known to occur in geographically discrete regions where virus transmission is primarily maintained among members of a single species or reservoir host. Spillover infection from these reservoirs to other animal species may occur in a

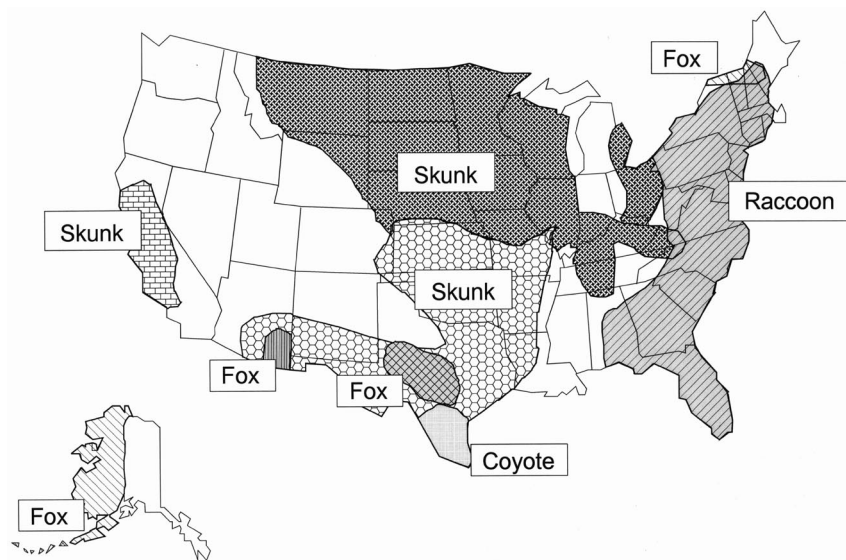


FIGURE 1. Distribution of major terrestrial reservoirs of rabies in the United States.

region, but such cases rarely initiate sustained intraspecific transmission. Once established, transmission within a species can persist at enzootic levels for decades, perhaps for centuries. Compartmentalization of the disease by species and geographic area has led to the evolution of distinctive variants of rabies virus that can be identified by reaction with panels of monoclonal antibodies¹⁰ or by patterns of nucleotide substitution identified by genetic analysis.¹¹ Temporally and spatially dynamic boundaries can be identified for both the principal animal reservoir for rabies, and VRV associated with the reservoir species (see FIGURE 1). Affected areas can expand but they may be bounded by natural barriers to animal movements, such as mountain ranges or bodies of water. However, unusual animal dispersal patterns or human-mediated translocation of infected animals can result in more rapid and unexpected introduction of the rabies virus into new areas.

Raccoons (*Procyon lotor*) have been recognized as a reservoir for the rabies virus in the Southeastern states since the 1950s. An outbreak that began during the late 1970s in the mid-Atlantic states has been attributed to the probable translocation by humans of infected raccoons from the long recognized epizootic in the Southeast.¹² Although described as separate epizootics, these two outbreaks have continued to expand and have now merged to include all of the Eastern coastal states, as well as Alabama, Pennsylvania, Vermont, West Virginia, and most recently, parts of Ohio.¹³

Three different VRVs are circulating in skunk reservoirs (*primarily Mephitis mephitis*) in the North central and South central states, and in California. A long standing reservoir for rabies virus is known in red and arctic foxes (*Vulpes vulpes* and *Alopex lagopus*, respectively) in Alaska. The disease spread during the 1950s to

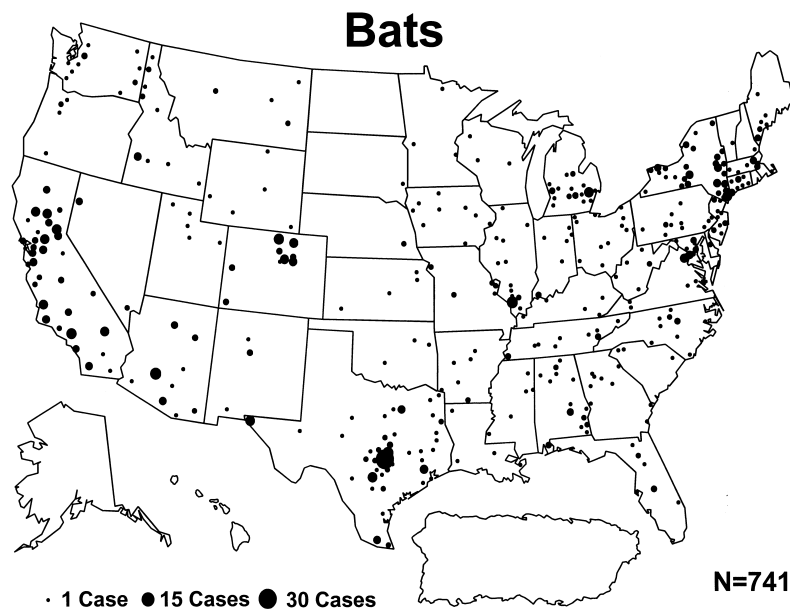


FIGURE 2. Reported cases of rabies in bats in the United States, by county, 1997.

include foxes across Canada and adjoining areas of the New England states. Rabies remains a persistent problem in foxes in Alaska, although reports of rabid foxes have declined in Canada, and foxes infected with this VRV are only intermittently reported in New England. Two different VRVs are present in small, discontinuous populations of gray foxes (*Urocyon cinereoargenteus*) in Arizona and Texas. An epizootic of rabies in coyotes (*Canis latrans*) and dogs in Southern Texas is the result of long standing interaction between unvaccinated domestic dogs and coyotes at the Texas–Mexico border.¹⁴

Geographic separation of these areas permits recognition of nine distinct geographic areas, each with its respective reservoir species (FIG. 1). In each of these areas, other terrestrial animals (including domestic species) acquire the disease, apparently as a result of spillover from these wildlife reservoir species.^{10,11} Multiple species of bats function as independent reservoirs for VRVs whose geographic ranges overlay the distribution of reservoirs in terrestrial animals (see FIGURE 2). At least 30 of the more than 39 species of bats that occur in the United States have been reported rabid at some time.¹⁵ A BAV associated with a single species of bat can be found throughout the range of a migratory species that may extend over thousands of miles.¹⁶

EPIDEMIOLOGY OF HUMAN RABIES

Between 1980, when potent and safe tissue culture-derived rabies vaccines were introduced in the United States, and 1998, rabies was diagnosed in 37 persons in the United States (see TABLE 1). Results of monoclonal antibody panels and genetic analyses indicated that the rabies infections in 12 of these individuals were caused by VRVs circulating in dog populations in foreign countries. Epidemiologic evidence also indicated that exposures occurred outside the United States.^{17–29} VRVs associated with the remaining human cases were known to exist in rabies reservoirs in the United States. This fact and other available epidemiologic evidence suggested that these remaining 25 infections were acquired in this country. All but three of these indigenously acquired infections were found to be caused by VRVs known to be maintained among insectivorous bats; in only one instance was there a definite history of animal bite.^{7,9,23,25,27,30–41} Two of the remaining three indigenous infections were the result of VRVs circulating in unvaccinated dogs and coyotes in South Texas, and one was the result of a VRV maintained by skunks in the North-central plains states CDC.^{23,27,31} BAVs were involved in two of the three human rabies cases that resulted from indigenously acquired infections during the decade 1980–1989. During the past decade through May 1999, BAVs were involved with 20 of the 22 human rabies cases of indigenously acquired infections. In the United States, the contribution of bats to the number of human rabies cases of indigenous origin (88%) is quite disproportionate to their contribution to the total number of cases reported annually (typically 600–1,000; 10%–11%).

With the emergence of bat-associated rabies as a public health problem have come some unique challenges for the prevention of human disease. From 1990–1998, histories of possible or actual bat contact were reported in several of the bat-associated cases, but there was clear evidence of a bite for only one (1990) of the 20

cases. History of physical contact with a bat was solicited from a family member or acquaintance, but no reliable history of bite was obtained. Lack of recognition of a bite or other contact known to be a risk factor for rabies virus transmission means that persons are not presenting themselves to health providers for evaluation and rabies postexposure prophylaxis (PEP). Although the exact nature of human–bat interaction resulting in rabies virus transmission remains unclear for the majority of these recent human cases, an undetected or unreported bat bite (deemed insignificant and not remembered) remains the most plausible hypothesis.

Low levels of clinical suspicion are linked to the lack of a clear exposure histories that health officials normally associate with rabies virus transmission. As an example, two of four human rabies cases in 1997 were originally suspected to be Creutzfeldt-Jacob disease (CJD). The tentative diagnoses of CJD resulted in the delay of postmortem examination of specimens and subsequent investigation for other humans potentially exposed. Rabies should be considered in the differential diagnoses of any patient with a presentation of encephalopathy of unknown etiology, even in the absence of a known animal bite as a possible source of rabies exposure.

A further unusual finding for human rabies cases since 1990 was the characterization in 15 (75%) of the 20 cases of a BAV that has been predominantly found in two species of bats, the silver-haired bat (*Lasiorycteris noctivagans*) and the Eastern pipistrelle bat (*Pipistrellus subflavus*). These species are rarely submitted for testing,⁴² although their ranges are extensive.⁴³ Because VRVs associated with a reservoir may spillover into other species, the identification of this BAV does not eliminate the involvement of species other than silver-haired and Eastern pipistrelle bats.

EXPLANATIONS AND TRENDS

The epidemiology of human rabies has change markedly. Dogs remain the major source of infection in most of the world, and the primary reservoir for all VRVs involved with human infections acquired outside the United States during 1981–1998. Vaccination of domestic animals, ongoing education programs, an efficient public health infrastructure, and wildlife vaccination programs have all but eliminated transmission of dog-associated VRVs to human beings within the United States. BAVs have replaced VRVs associated with dogs as the primary cause of human rabies infections in this country. Explanations for the increasing recognition of BAVs as the source of human disease include unique behavior of the infected species involved in transmission and unique adaptations of silver-haired/Eastern pipistrelle BAV that allow infection and replication under broader ranges of conditions than other VRVs,⁴⁴ as well as advances in technology that permit this BAV to be distinguished from others.

Absence of “traditional” bite histories hinders exposure assessment and recommendations for rabies PEP. New public health challenges resulting from the changing epidemiology of rabies in the United States have led to modification of previous recommendations of the Advisory Committee on Immunization Practices (ACIP) relating to rabies exposure. The new ACIP recommendations state that PEP “should be considered when direct contact between a human and a bat has occurred, unless the exposed person can be certain a bite scratch, or mucous membrane exposure did

TABLE 1. Cases of rabies in human beings in the United States, by circumstances of exposure and rabies virus variant, 1980 to 1998^a

Date of death	State of residence	Exposure history ^b	Rabies virus variant ^c
12 Aug 81	AZ	Dog bite–Mexico	Dog, Mexico
4 Sep 81	OK	Unknown	Skunk, South Central
18 Jan 83	MA	Dog bite–Nigeria	Dog, Nigeria
9 Mar 83	MI	Unknown (Contact?)	Bat, Ln/Ps
7 Jul 84	TX	Unknown–Laos	Dog, Laos
29 Sep 84	PA	Unknown	Bat, Msp
1 Oct 84	CA	Dog bite–Guatemala	Dog, Guatemala
20 May 85	TX	Unknown–Mexico	Dog, Mexico
15 Dec 87	CA	Unknown–Philippines	Dog, Philippines
3 Feb 89	OR	Unknown–Mexico	Dog, Mexico
5 Jun 90	TX	Bat bite–TX	Bat, Tb
20 Aug 91	TX	Unknown	Dog/coyote
25 Aug 91	AR	Unknown (Contact)	Bat, Ln/Ps
8 Oct 91	GA	Unknown (Contact?)	Bat, Ln/Ps
8 May 92	CA	Dog bite–India	Dog, India
11 Jul 93	NY	Unknown (Contact?)	Bat, Ln/Ps
9 Nov 93	TX	Unknown	Bat, Ln/Ps
21 Nov 93	CA	Dog bite–Mexico	Dog, Mexico
18 Jan 94	CA	Unknown	Bat, Ln/Ps
21 Jun 94	FL	Unknown–Haiti	Dog, Haiti
11 Oct 94	AL	Unknown (Contact)	Bat, Tb
15 Oct 94	WV	Unknown (Contact)	Bat, Ln/Ps
23 Nov 94	TN	Unknown (Contact?)	Bat, Ln/Ps
27 Nov 94	TX	Unknown	Dog/coyote
15 Mar 95	WA	Unknown (Contact?)	Bat, Msp

TABLE 1/continued.^a

Date of death	State of residence	Exposure history ^b	Rabies virus variant ^c
21 Sep 95	CA	Unknown (Contact)	Bat, Tb
23 Oct 95	CT	Unknown	Bat, Ln/Ps
9 Nov 95	CA	Unknown (Contact?)	Bat, Ln/Ps
8 Feb 96	FL	Dog bite–Mexico	Dog, Mexico
20 Aug 96	NH	Dog bite–Nepal	Dog, SE Asia
15 Oct 96	KY	Unknown	Bat, Ln/Ps
19 Dec 96	MT	Unknown	Bat, Ln/Ps
5 Jan 97	MT	Unknown (Contact?)	Bat, Ln/Ps
18 Jan 97	WA	Unknown (Contact?)	Bat, Ef
17 Oct 97	TX	Unknown (Contact)	Bat, Ln/Ps
23 Oct 97	NJ	Unknown (Contact)	Bat, Ln/Ps
31 Dec 98	VA	Unknown	Bat, Ln/Ps

^aAll laboratory confirmed cases of rabies in human beings who developed the disease in the United States through 1998. Excluded are three people who were exposed to the disease and died of their infections while outside the United States and for whom no rabies virus isolates were available.

^bData for exposure history are reported only when the biting animal was available and tested positive for rabies; or when plausible information was reported directly by the patient (if lucid or credible); or when a reliable account of an incident consistent with rabies exposure (e.g., dog bite) was reported by an independent witness (usually a family member).

^cVariants of the rabies virus associated with terrestrial animals in the United States are identified with the name of the animal reservoir, whereas variants of the rabies virus acquired outside the United States are identified with the names of the reservoir animal (dog, in all cases shown), followed by the name of the most definitive geographic entity (usually the country) from which the variant has been identified. Variants of the rabies virus associated with bats are identified with the names of the species of bat(s) in which they have been found to be circulating. In some instances the known or presumed geographic location of human beings when they were infected may rule out one of the species indicated in for the variant known as the silver-haired/pipistrelle variant (Ln/Ps). Because information regarding the location of the exposure and the identity of the exposing animal is almost always gathered retrospectively and much information is frequently unavailable, the location of the exposure and the identity of the animal responsible for the infection are often limited to deduction.

NOTE: Ln/Ps, *Lasionycteris noctivagans* or *Pipistrellus subflavus*, the silver-haired bat or the Eastern pipistrelle; Msp, *Myotis*, species unknown; Tb, *Tadarida brasiliensis*, the Brazilian (Mexican) free-tailed bat; Ef, *Eptesicus fuscus*, the big brown bat.

not occur.” and when a bat is found indoors, PEP “can be considered for persons who were in the same room as the bat and who might be unaware that a bite or direct contact” (with bite a possible result) “had occurred (e.g., a sleeping person awakens to find a bat in the room or an adult witnesses a bat in the room with a previously unattended child, mentally disabled person, or intoxicated person) and rabies cannot be ruled out by testing the bat.”⁴⁵ There are no data suggesting that non-bite transmission of rabies virus from bats has occurred but the events leading to human exposures remain elusive.

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