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MAMMALIAN RESERVOIRS AND THE CHANGING EPIDEMIOLOGY OF RABIES IN THE UNITED STATES

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ABSTRACT: The epidemiology of rabies in the United States has changed dramatically over the past few decades. Greater than 90% of all animal rabies cases reported annually to the Centers for Disease Control and Prevention now occur in wildlife, whereas before 1960 the majority were domestic animals. The principal rabies reservoirs today are wild carnivores and bats, infected with many different types of rabies virus variants. Annual reporting of human deaths have fallen from more than 100 at the turn of the century to one to six per year, despite major outbreaks of animal rabies in several distinct geographic areas. Most recent human rabies cases acquired in the United States are the result of infection with rabies virus variants associated with bats, although the exact incident leading to exposure has been difficult to define. Many recent deaths have occurred in persons who failed to seek post-exposure treatment, presumably because they did not recognize a risk in the animal contact leading to the infection or failed to recognize that contact had occurred. Although these human rabies deaths are rare, estimated public health costs associated with disease detection, prevention, and control have risen, exceeding millions of dollars each year.

KEY WORDS: rabies, animal bites, raccoons, bats, skunks, vaccination, epidemiology

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INTRODUCTION

Perhaps the oldest recognized zoonotic disease, rabies continues to cause >35,000 deaths annually. These potentially preventable deaths occur primarily in Asia, Africa, and Latin America, where most of the virus transmission to humans results from bites inflicted by rabid dogs (WHO 1993). In contrast, in the United States and other developed nations, animal control and vaccination programs coupled with effective and widely available biologics for post-exposure prophylaxis (PEP), have reduced the annual number of human rabies deaths to a few per year. The epidemiology of rabies in the United States has changed radically since the era when dog rabies predominated (Held et al. 1967). Human exposures and disease are still ultimately linked to cycles of rabies virus transmission in animals, however, wildlife now make the greatest contribution to annual total rabies cases in the United States (Figure 1; Krebs et al. 1997). It is probable that the incidence of rabies in humans in the United States has approached a level that cannot be further reduced without targeting wildlife for rabies control. However, even if rabies virus was eliminated in terrestrial carnivores, human deaths would not be reduced to zero because for the last decade the majority of human cases have been associated with variants of rabies virus maintained in a chiropteran reservoir (Noah et al. 1998).

METHODS AND RESULTS

Rabies Virus and Reservoir Hosts

Rabies virus is one of six (or seven if the Pteropid bat virus from Australia receives serotype/genotype status [Speare et al. 1997]) virus serotypes/genotypes in the genus *Lyssavirus* (family Rhabdoviridae) (Bourhy et al. 1993). This family is one of three in the Order Mononegavirales, which is made up of agents with single stranded negative sense RNA genomes. Several of the lyssavirus serotypes/genotypes have been associated with

neurotropic disease in humans and animals including Mokola, Duvenhage, European bat lyssavirus types I and II, and Pteropid bat virus (Meredith et al. 1971; Familusi et al. 1972; Selimov et al. 1989; Fraser et al. 1996). Rabies (serotype/genotype 1) virus has a near global distribution, with the exceptions of Antarctica and Australia.

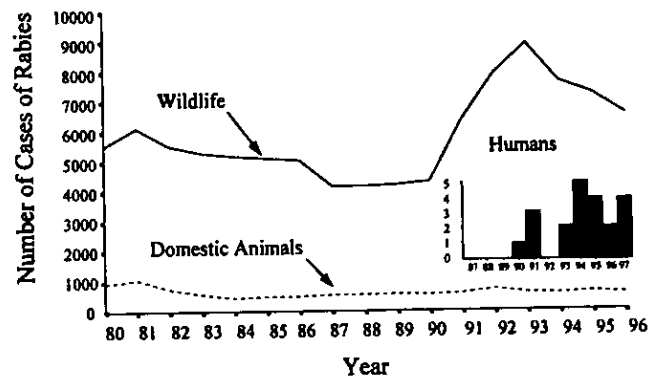


Figure 1. The trend in reported rabies cases shows wildlife to be the principal reservoir of rabies virus in the United States. The increase in reported wildlife cases during the 1990s has been primarily associated with an epizootic of rabies in raccoons in the eastern United States. The number of human rabies cases acquired within the United States has shown an apparent increase since the mid-1980s, unrelated to the increase in rabies in terrestrial carnivores.

Over the past 20 years, an understanding of epidemiologic patterns of rabies virus maintenance in natural populations has occurred through advances in immunology and molecular biology. Applications of monoclonal antibodies for antigenic typing and genetic sequence analyses of rabies virus variants have defined enzootic maintenance cycles of unique variants of rabies virus primarily associated with a single species of mammal (the reservoir host) within geographic regions in the United States (Rupprecht et al. 1987; Smith 1989; Smith and Seidel 1993). Within these defined regions, these unique variants of rabies virus can be recovered from multiple species of mammals infected by transmission from the primary reservoir host, but this "spillover" does not typically result in adaptation of the variant to additional host species and subsequent independent maintenance cycles. This association of virus and host means that the spatial distributions of rabies variants in specific mammalian carnivores have distinct geographic boundaries which can be mapped using data submitted to the Centers for Disease Control and Prevention (CDC) by state and territorial rabies laboratories (Krebs et al. 1996; Krebs et al. 1997). These data and maps provide valuable information on the distribution of endemic or epidemic rabies in animals, and over time provide a dynamic view of the how this virus spreads through and influences host populations. Overlaying the distribution of rabies viruses in terrestrial mammals are multiple, independent reservoirs for rabies virus in numerous species of insect-eating bats in the United States. At least 30, of the approximately 39 species of bats which occur in the United States, have been found to be rabid at some time (Constantine 1979). Patterns in the distributions of bat-associated rabies virus variants can be more difficult to detect as many species of bats are migratory and populations are thus intermixed (Smith 1988). This surveillance information is of tremendous importance to local and state health departments for planning annual budgets related to rabies prevention and to prepare for control measures directed at owned animals and wildlife.

The current distribution of the major variants of rabies virus and their associated terrestrial wildlife hosts cover much of the continental United States (Figure 2). Once established within a particular animal population, rabies virus transmission can persist for decades, perhaps for centuries. Rabies has been enzootic in Arctic fox (*Alopex lagopus*) and red fox (*Vulpes vulpes*) populations of Alaska and New England, respectively, and in raccoon (*Procyon lotor*) populations of the southeastern states for at least 50 years. Annual fluctuations in the numbers of rabid animals reported from specific locales are the rule, but frequently the disease persists at low levels (enzootic). Rabies virus can also cause sensational epizootics, as occurred in raccoon populations along the eastern seaboard of the United States over the last two decades (Anonymous 1997a). The outbreak was believed to have been initiated when infected raccoons originating from the established southeastern focus of rabies in raccoons were translocated to the mid-Atlantic region for hunting and trapping (Nettles et al. 1979). Since the mid-1970s, a rabies variant highly adapted to raccoons has spread from the mid-Atlantic region to Maine, and caused one of the

most intensive epizootics of animal rabies ever recorded (Figure 3). The magnitude of this epizootic was enhanced by the spread of virus through naive raccoon populations of very high density, sometimes in states which had not experienced terrestrial rabies for decades (Rupprecht and Smith 1994).

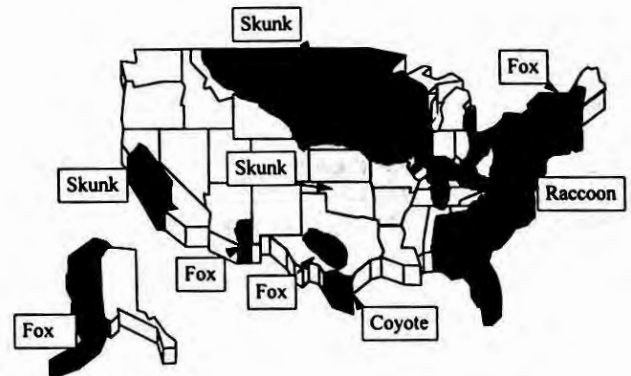


Figure 2. Distribution of the endemic areas for various rabies virus variants with their major terrestrial reservoirs in the United States.

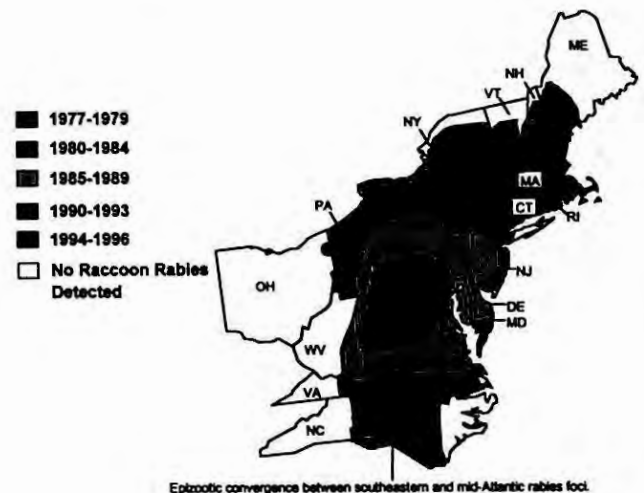


Figure 3. Expansion of the area of the eastern United States affected by the epizootic of rabies in raccoons. Rabies virus was presumably introduced into the West Virginia/Virginia region in the mid-1970s.

The natural accumulation of mutations in rabies virus that results in distinctive virus variants in spatially "isolated" carnivore populations, also occurs with rabies variants associated with bats. However, the behavior of bats complicate attempts to define neat geographical boundaries to a particular variant range. A virus variant associated with a particular bat species can be found throughout a migratory range that may extend over thousands of miles (Baer and Smith 1991). For example, rabies virus associated with Mexican free-tailed bats

(Tadarida brasiliensis) shows minimal sequence variation in samples collected in Florida, Alabama, Texas, New Mexico, Nevada, Colorado, and California. Similarly, samples from the migratory silver-haired bat (*Lasiurus noctivagus*) in New York, Wisconsin, Washington, Colorado, and California are nearly identical. All areas of the United States, with the exception of Alaska and Hawaii, are home to a variety of different bat species affected by rabies. These associations result in enzootic rabies in the continental United States in several different bat species, each transmitting a distinct rabies variant.

The Epidemiology of Human Rabies

Human rabies cases diagnosed in the United States declined from 10 to 12 cases annually at the end of World War II to one to two cases per year by 1990 (Held et al. 1967; Anderson et al. 1984). Unfortunately, since 1990 this number again appears to be on the rise (Figure 1), which is presumably the result of a variety of changes in the epidemiology of this disease (Noah et al. 1998). Of primary concern in recent decades is the increasing recognition of variants of rabies virus associated with a bat reservoir as important causes of human rabies. During the period from 1990 to 1997, 19 of the 21 cases of human rabies believed to have been acquired through exposures received in the United States were attributable to a viral variant associated with bats (Noah et al. 1998). The two remaining cases were attributable to rabies virus variants circulating in dogs and coyotes in the southwestern United States. Five additional cases were diagnosed in individuals who had lived or traveled abroad and received their exposure to rabies virus in another country. The viruses characterized from persons exposed in another country were all linked to variants circulating in dogs and endemic to the particular region where exposure occurred.

With the recognition of bat-associated rabies have come some unique challenges for the prevention of disease. In only one of the 19 bat-associated cases of human rabies reported from 1990 to 1997 was there clear evidence of bite. In several cases, a history of physical contact with a bat was reported by the patient or a family member, but no reliable history of bite was obtained. This lack of recognition of a bat bite or other contact known to be a risk factor for rabies virus transmission means that persons are not presenting to health providers for rabies PEP. Although the exact nature of human-bat contact resulting in rabies virus transmission remains unclear for many recent human cases, an undetected or an unreported bat bite remains the most plausible hypothesis. Rabies virus transmission other than by bite is rare and occurs under exceptional circumstances such as tissue (corneal) transplantation (Houff et al. 1979), accidental laboratory aerosolization of concentrated virus (Winkler et al. 1973), or exposure to aerosolized virus in caves inhabited by millions of bats (Constantine 1962).

An additional problem in the changing epidemiology of human rabies is the low level of clinical suspicion and timing of diagnosis, which may be linked to the lack of a clear exposure history health professionals normally associate with rabies virus transmission. As a result of

this unclear history of exposure, many rabies cases are now being diagnosed postmortem. Two of the four rabies cases in 1997 were originally suspected to be Creutzfeldt-Jakob disease, delaying postmortem diagnosis and follow-up of other potentially exposed humans for weeks (Anonymous 1997b). In addition to the lack of bite history, the rarity of rabies in the United States makes diagnosis difficult. Any patient who presents with an encephalopathy of unknown etiology should be considered a potential rabies case, even in the absence of known rabies exposure through animal bite.

A final unusual finding in the cases of human rabies in the United States since 1990, was the identification of a rabies virus variant in 14 (74%) of the 19 cases as one almost exclusively found in either the silver-haired bat (*L. noctivagus*) or the eastern pipistrelle (*Pipistrellus subflavus*). These species of bats are rarely submitted for rabies testing (Childs et al. 1994) although their geographic ranges are extensive (Nowak 1994). Because rabies virus variants associated with a reservoir can also be found in other species during "spillover" events, the identification of a variant indicates the ultimate reservoir, if not the proximate animal source of infection.

Control and Prevention

Rabies PEP is expensive and not without risk of adverse reactions (Fishbein et al. 1989). Typically, increases in animal rabies result in increases in numbers of PEPs, and frequently rabies control programs aimed at reducing rabies in wildlife must be justified on the basis of potential cost savings. As an example, in New York State, the estimated number of persons receiving PEP increased from 84 in 1989, prior to the reintroduction of terrestrial rabies due to raccoons, to 1,125 in 1992 and 2,905 in 1993 (Anonymous 1994).

Interventions aimed at either reducing the incidence of rabies in wildlife or preventing the spread of rabies are ongoing in several states. Most of these programs are using a vaccinia-rabies glycoprotein (V-RG) recombinant virus vaccine as the vehicle to immunize animals. Similar programs using a variety of different vaccine types have been very effective in reducing the incidence of red fox rabies over much of western Europe (Pastoret et al. 1995). In the United States the efficacy of programs using V-RG contained within baits for ingestion by raccoons is under assessment in eastern Massachusetts (Cape Cod), eastern and northern New York State, southern New Jersey (Cape May), Florida (Pinellas County) and, most recently, Vermont and Ohio (Columbiana, Mahoning, and Trumbull counties) (Hanlon and Rupprecht 1998). Results of earlier trials designed to determine vaccine safety, efficacy, ecologic impact, and physical bait variables have been favorable (Rupprecht et al. 1988; Hable et al. 1992; Rupprecht et al. 1993; Hanlon and Rupprecht 1998). The V-RG virus vaccine was fully licensed in April 1997 for use in raccoons. In Texas, the same V-RG vaccine, packed in different bait, is being used for the potential control of rabies in both coyotes and gray foxes (Meehan 1995). Oral rabies vaccine distribution in each state is limited to authorized state or federal rabies control programs (Jenkins et al. 1998).

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