CURRENT ISSUES IN RABIES PREVENTION IN THE UNITED STATES

Health Dilemmas, Public Coffers, Private Interests

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SYNOPSIS

OVER THE LAST 100 years, rabies in the United States has changed dramatically. More than 90% of all animal rabies cases reported annually to the CDC now occur in wildlife, whereas before 1960 the majority were in domestic animals. The principal rabies hosts today are wild carnivores and bats infected with several viral variants. Annual human deaths have fallen from more than a hundred at the turn of the century to one to two per year despite major outbreaks of animal rabies in several geographic areas. Modern day prophylaxis has proven nearly 100% successful; most human fatalities now occur in people who fail to seek medical treatment, usually because they do not recognize a risk in the animal contact leading to the infection. Although these human rabies deaths are rare, the estimated public health costs associated with disease detection, prevention, and control have risen, exceeding millions of dollars each year. Cost considerations must be weighed along with other factors in addressing issues such as the appropriate handling of nontraditional and exotic pets, future guidelines for rabies prophylaxis, and novel methods of disease prevention.

Few diseases have the same ability to command public attention as rabies, an acute viral encephalomyelitis. The word "rabies" quickly brings to mind those apocryphal childhood tales of an unfortunate person mauled by a mad dog and forced to undergo that painful and now historical series of 14 to 21 "shots in the stomach." Perhaps it is the episodic media attention paid to this horrible topic that results in vivid mental snapshots like the heart-wrenching demise of Old Yeller in America's frontier environment, the cool steady dispatch of a slavering canine by Atticus Finch in the small Southern town depicted in *To Kill A Mockingbird*, and the maniacal rampage of the brutish St. Bernard Cujo. Yet, today, while dog bites are certainly common in the United States,[1] few will experience dog rabies firsthand due to significant advances in dog control and rabies prevention over the last 50 years. One is much more likely to encounter rabies in many urban areas of Africa, Asia, or Latin America[2] than in the United States.

While in the past the primary rabies concern in this country involved domestic animals, of late there has been a resurgence of rabies among native wildlife. This means that a person may be indirectly exposed to rabies if the family dog fights with a raccoon or the pet cat dutifully presents a captured bat. Increases in wildlife rabies are partially related to human demographics, animal translocations, ecological alterations, and viral adaptations.[3] Expanded knowledge of the properties and natural history of rabies, reinforced by the application of common sense and appropriate preventive action,[4,5] will greatly minimize the risk of exposure and of acquisition of the disease. Yet common childhood fears persist.

Human rabies cases declined from 10 to 12 cases annually at the end of World War II to one to two cases per year by the 1990s. So, is the public health attention to rabies warranted? An extensive prevention effort has been effective in minimizing human fatalities, with the programmatic cost assumed by local, state, and Federal governments and much of the costs associated with rabies vaccination (animal and human) borne by the public. Although only 28 cases of human rabies were diagnosed in the United States during the period from 1981 to 1995, exposures—and perceived exposures—to potentially rabid animals result in tens of thousands of people receiving rabies postexposure prophylaxis (PEP) each year. Unnecessary treatment with PEP has been identified as a major problem.

Virus, Host, and Environment

In the late stages of the disease, rabies virus spreads from the brain to the salivary glands. Outbreaks of rabies occur primarily by bite transmission of infectious virus in the saliva and are usually characterized by transmission between animals of the same species. Although other mammals may be infected through contact with these host species, such cases remain sporadic. The disease tends to persist at low levels (enzootic) rather than be explosive and sharply cyclical (epizootic); once the disease is established within a particular animal population, transmission can persist at low levels for decades or, perhaps, centuries.

For example, in areas of the Western states where the striped skunk (*Mephitis mephitis*) is an important reservoir of the virus, rabies was so common in the late 19th century that two to three foot high canvas "skunk boats" were marketed with tents as protection from nocturnal attacks by rabid skunks on the Plains, for "...a man in a bedroll to pass the night without fear...."[6] Rabies has also been enzootic in the Arctic fox (*Alopex lagopus*) population of Alaska and the red fox (*Vulpes vulpes*) population of New England and in raccoon (*Procyon lotor*) populations of the southeastern states for at least 50 years.

The translocation of infected animals from the southeastern states to the mid-Atlantic region for hunting and trapping during the late 1970s is thought to have led to an intensive rabies outbreak among raccoons that continues to the present.[7] Thus, the disease in this country is a modern composite involving raccoons, skunks, foxes, coyotes, bats, and the species they encounter (Figure 1).

When virus populations are sequestered or isolated, the natural accumulation of mutations creates distinctive variants, which can be identified by molecular techniques. Analysis of rabies virus RNA has identified a large number of viral variants,[8] each associated with a certain mammal species or a geographic area (Figure 2). Outbreaks of rabies in carnivores tend to have discrete geographic boundaries that can be easily displayed on surveillance maps.[9] Overlaying the disease in terrestrial mammals are multiple, independent reservoirs for rabies in several species of insect-eating bats. As is true for terrestrial species, distinct viral variants can be identified for different bat species. Unlike in terrestrial animals, however, specific geographic boundaries cannot be defined for bat rabies.

A variant associated with a particular bat species can be found throughout a migratory range that may extend over thousands of miles. For example, rabies virus transmitted by the migratory freetail bat (*Tadarida brasiliensis*) shows minimal variation in samples collected in Florida, Alabama, Texas, New Mexico, Nevada, Colorado, and California. Similarly, samples from the migratory silver-haired bat (*Lasionycteris noctivagans*) in New York, Wisconsin, Washington, Colorado, and California are nearly identical.[8]

All areas of the United States, with the exception of Alaska and Hawaii, are home to a variety of bat species affected by rabies. Each of these species transmits a distinct variant of rabies virus (Figure 2).

Inexplicable Human Fatalities

From 1980 to date, between 600 and 1000 cases of rabid bats have been reported annually (with a median of 726), usually peaking seasonally in the late summer and early autumn months.[9] Current surveillance efforts show that there has not been an increased incidence of the disease

among bat populations; the proportion that are rabid among bats submitted to diagnostic laboratories ranges typically from only 5% to 15%. Moreover, the occurrence of bat rabies appears largely independent of rabies in terrestrial carnivores, although viral spillover to animals other than bats does occasionally occur.[10] In perspective, the public health significance of bats as reservoirs of zoonotic disease is small in comparison to the ecological benefits they provide: aerial insect predation, pollination, and seed dispersal.

Still, bats have accounted for an increasing proportion of the rabies virus transmitted from wildlife to humans in recent years.

From 1980 to 1995, 15 of the 28 cases of human rabies diagnosed in the United States resulted from infection with variants of rabies viruses associated with bats. In 10 of the 15 bat-associated human cases, the variant identified was transmitted by the silver-haired bat (*L. noctivagans*). Silver-haired bats are a solitary, migratory species uncommonly seen in the laboratory for rabies diagnosis and with a preferred habitat of old growth forest.

Investigations of recent human rabies cases indicate that people may not realize that they have been bitten by bats and that even apparently limited contact with rabid bats may result in transmission to humans.[11] For example, in one recent case, a bat killed in a child's room was later found to be rabid, but only after the child was in the late stages of the disease. The child had been asleep when the bat was found and no bite was immediately evident when she was examined. Bat teeth are small but sharp, and the wound they inflict may not draw blood or be immediately noticed. Only one of the recent 15 human rabies cases had a clear history of exposure due to a bat bite,[12] although many of the patients reported some physical contact with a bat. Some virus variants found in bats are thought to possess special characteristics that support infectious transmission even under limited conditions.[13]

For bats, as with other high risk mammals such as raccoons, skunks, foxes, and coyotes, rabies PEP is recommended for people with bite, scratch, or mucous membrane exposure unless the animal is available for testing and is negative for rabies. The inability of care providers to elicit information about potential exposures involving bats has been especially troublesome given the recent trend in human rabies in the United States. Documentation of conventional exposures leading to bat-transmitted rabies may be hampered by the limited injury inflicted by a bat bite (in comparison to lesions inflicted by terrestrial carnivores) or by circumstances that hinder accurate recall of events. Therefore, public health professionals have recently decided that PEP is also appropriate in situations in which there is reasonable probability that a bite or scratch occurred, even in the absence of a demonstrable contact—for example, when a sleeping person awakes to find a bat in the room, an adult witnesses a bat in the room with a previously unattended child, or a bat is found in the presence of a mentally challenged or intoxicated person. This recommendation, used in conjunction with current ACIP guidelines,[4] should maximize a provider's ability to respond to situations in which accurate exposure histories may not be obtainable while still minimizing inappropriate PEP.

Many of the concerns over publicizing such recommendations about unrecognized bat exposures are legitimately based on cost considerations. Some states reimburse the costs of rabies PEP, and state public health planners are hesitant to initiate costly changes without a proven preventive benefit. At this time, data on PEP use and the likely effects of recommended changes are unavailable.

Beyond enhanced scrutiny, continued rabies prevention efforts should include public warnings against handling wildlife, prompt and proper medical evaluation of animal bites, offering pre-exposure rabies immunization to those at vocational risk, and continuing to vaccinate "companion animals."

Enter the Exotic Pet

Issues concerning the threat of rabies are frequently emotionally charged. Public health officials must weigh the consequences of euthanizing a valued family pet against the risks of avoiding or delaying critical, albeit costly, human PEP for what without treatment is an invariably fatal illness.

These difficult considerations become even more onerous when the specter of rabies is used to advance other concerns or interests. As a result, the legitimate debate over

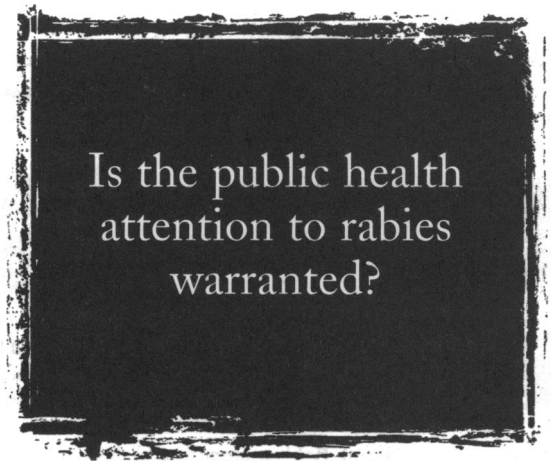
Table. Reported cases of rabies in ferrets, United States, 1958 to present

Year	State	Human bite
1958	Kentucky	Unknown
1978	South Carolina	Yes
1981	North Dakota	No
1982	Kansas, Virginia	Yes
1983	Wisconsin	Yes
1985	California, Michigan	Yes
1986	District of Columbia	No
	North Dakota	No
	South Carolina	Yes
1987	District of Columbia	No
	Iowa	Yes
1992	South Carolina	Yes
	Virginia	No
1993	Virginia	Yes
1994	Maryland	No
1995	Connecticut	Yes
	New York	No
1996	Florida	Yes
	Arkansas	No

Although national ferret societies report more than one million ferrets maintained as pets, only 20 rabid ferrets have been documented since 1958.

rabies prevention and the handling of pets involved in possible human exposures has been complicated. Issues range from the suitability of certain species as house pets to somewhat arcane and controversial questions about taxonomic revision. Intense private and public lobbying efforts can drive some public health deliberations, channeling time and scarce resources into relatively esoteric research. One such controversy has involved the acquisition of animals such as ferrets and wolf hybrids as pets.

Ferrets. The European ferret (*Mustela putorius*) has grown in popularity as a companion animal, but little is known about how the virus causes disease in this species. Although national ferret societies report annual sales exceeding 50,000 animals and more than one million are maintained as pets in the United States, rabies is rarely reported in ferrets. Since 1958, only 21 rabid ferrets have been documented by CDC through national surveillance activities. (Table 1).



An important and often-asked question is whether ferrets, which are known to have bitten small children, make appropriate domestic pets.[14] This issue should be considered separately from concern over the animal's potential role in rabies transmission. However, once the issue of rabies was raised in the debate over ferret ownership, a number of studies were designed to investigate the pathogenesis of rabies in ferrets to provide scientific guidelines in the event of ferret bite. While such information is available for cats and dogs,[15] the virus shedding period of an infected ferret is unknown. Hence, ferrets that bite are frequently euthanized rather than quarantined, even if the ferret has been vaccinated.[16]

In a preliminary study[17] designed to investigate the transmission and clinical course of rabies—a study that can be followed as an example in other species—50 ferrets were inoculated with street rabies virus of skunk origin. Susceptibility was shown to be directly related to the inoculation dose of rabies virus, and the incubation period was found to be inversely related to dose. Incubation periods ranged from two weeks to more than three months. The typical clinical presentation included paresthesia, fever, hyperactivity, weight loss, ataxia, and ascending paralysis. Morbidity periods were approximately four to five days. Rabies antigen was detected upon examination of brain tissue of 33 clinically rabid ferrets by immunofluorescent microscopy; 16 ferrets remained clinically normal and were negative for rabies antigen at necropsy. Rabies virus was not isolated from any oral swabs, but was recovered from a salivary gland collected at necropsy from one rabid ferret. The proportion of ferrets that developed rabies virus neutralizing antibodies (VNA) was directly related to the inoculum dose and usually appeared concomitantly with clinical signs. One ferret that presented with clinical signs of rabies seroconverted and eventually recovered but with severe paralytic sequelae; VNA were detected in the cerebrospinal fluid. These preliminary data are based on a single rabies variant of skunk origin but are in agreement with a prior investigation utilizing a European red fox rabies variant.[18]

These studies suggest that ferrets are not idiosyncratic in their response to rabies infection and that quarantine and observation periods may be reasonable to consider as additional data become available. Several states have already initiated quarantines for ferrets. Clearly, the pathogenesis of rabies, including viral excretion, may vary depending upon the dose, the route, and the strain of virus.[19] While the likelihood of rabies in ferrets may be low,[20] caution is warranted.

Wolves and wolf hybrids. Rabies management and prevention in wolves and wolf hybrids maintained as pets is under active discussion. Reports of rabies in wolves are infrequent and the epizootiology of rabies in these canids is poorly understood because cases occur primarily in sparsely populated circumpolar regions of North America and Eurasia and portions of the Middle East.[21] Cases of rabies in wolves in the United States have been reported primarily from Alaska, averaging less than one per year from 1980 to date. Only two cases of rabies in wolf hybrids have been reported from the United States, both from California. No rabies vaccine is currently licensed for parenteral use in wolves or in any captive wild animal.[5]

Recently, suggested taxonomic revisions[22] have collapsed the former species designations *Canis familiaris* (the domestic dog) and *C. lupus* (the gray wolf) within the *Canis* genus, providing additional grounds for wolf-hybrid proponents that their animals be treated as dogs if they bite people or in recommendations concerning rabies vaccination. Taxonomic revisions of this type are commonly controversial, and legitimate concern arises over the alteration of rabies recommendations solely on their basis.

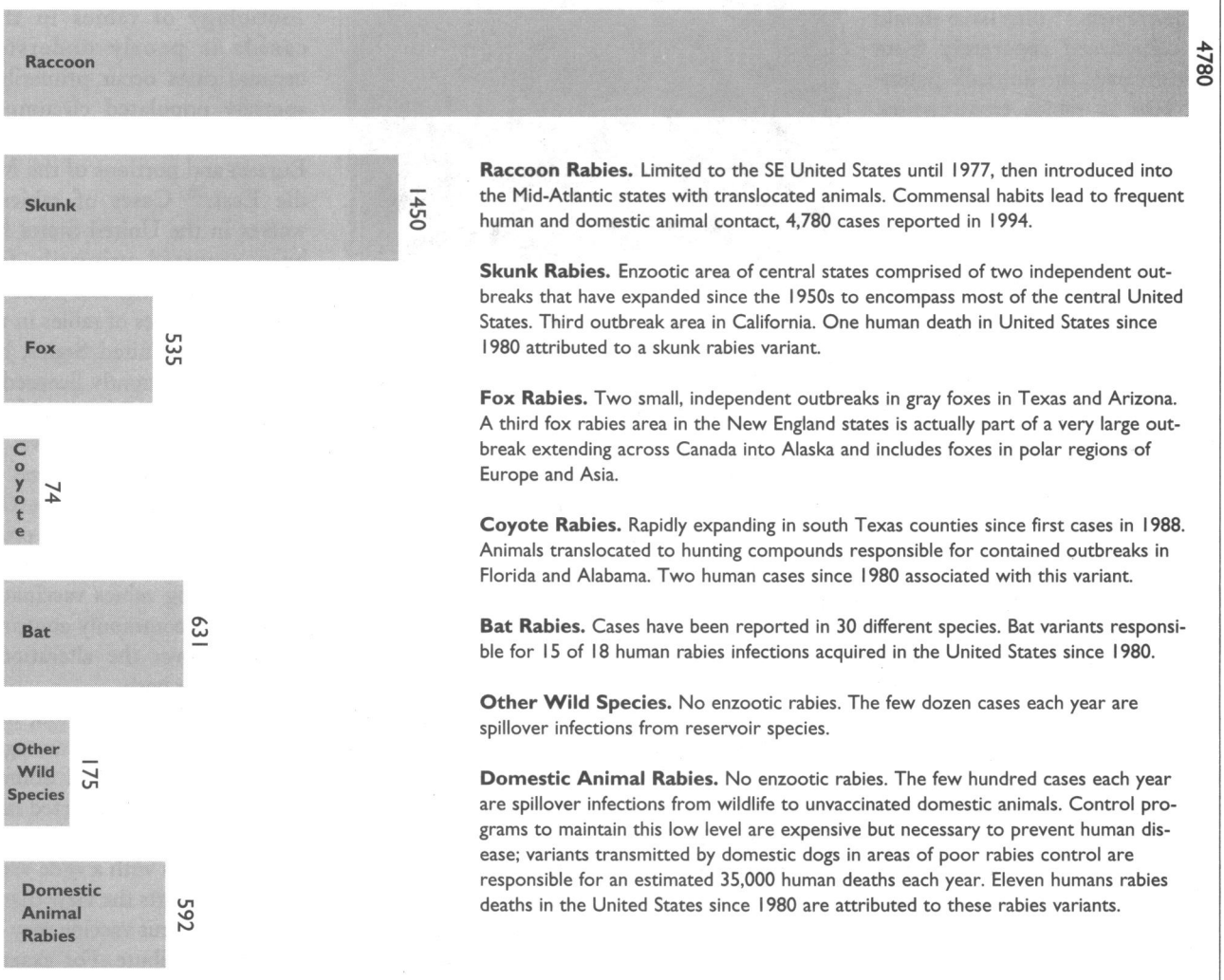
Although no vaccine offers complete protection, modern cell culture vaccines are extremely potent immunogens. Their widespread use has effectively eliminated domestic dog rabies in the United States, reducing the reported rabies cases in dogs from more than 9000 in 1944 to 146 by 1995. Moreover, comparative vaccination trials with a wide variety of taxonomically disparate species supports the view that the overall mammalian response to rabies virus vaccine may be a rather conservative immunological attribute. For example, current rabies products licensed in the United States provide

demonstrable efficacy for representatives of at least six different mammal families.[5] Additionally, preliminary review of the serological response of wolves to parenteral rabies vaccination does not reveal significant overall differences from the response of the domestic dog.

These combined data suggest that if wolves and wolf hybrids are vaccinated at three months of age with a USDA-licensed, inactivated cell culture rabies vaccine, are administered a booster vaccination one year later, and are promptly revaccinated annually or triennially, they should respond appropriately. A 1993 case in California of rabies in a young wolf hybrid[23] likely infected by a rabid skunk approximately six months after a single rabies vaccination does not necessarily signify the failure of rabies immunization for these animals; it rather underscores the recommendation for immediate booster administration following any suspected rabies exposure in a currently vaccinated animal together with observation for at least 45 days thereafter.

Nevertheless, the question of vaccination is not the only rabies-related issue of public health significance with regard to wolves and wolf hybrids. Wolf bites tend to be broad, deep, multiple and often involve severe wounds to the head, again triggering debate as to the suitability of these animals as domestic pets except under special circumstances. Currently, a domestic dog involved in human exposure can be quarantined and observed over a 10-day period; if the animal remains healthy, costly human rabies PEP may be avoided. The experience gained from dog rabies control programs in the United States during the past 50 years may not be relevant; the subtle behavioral alterations and associated clinical manifestations indicative of viral encephalitis may not be as readily apparent in a rabid wolf. Infected wolves have traditionally been recog-

Various mammal hosts are responsible for perpetuating the spread of rabies throughout the United States. In 1994, raccoons, skunks, foxes, coyotes, and bats represented most of the 8224 animals diagnosed with rabies at local public health laboratories.



Raccoon Rabies. Limited to the SE United States until 1977, then introduced into the Mid-Atlantic states with translocated animals. Commensal habits lead to frequent human and domestic animal contact, 4,780 cases reported in 1994.

Skunk Rabies. Enzootic area of central states comprised of two independent outbreaks that have expanded since the 1950s to encompass most of the central United States. Third outbreak area in California. One human death in United States since 1980 attributed to a skunk rabies variant.

Fox Rabies. Two small, independent outbreaks in gray foxes in Texas and Arizona. A third fox rabies area in the New England states is actually part of a very large outbreak extending across Canada into Alaska and includes foxes in polar regions of Europe and Asia.

Coyote Rabies. Rapidly expanding in south Texas counties since first cases in 1988. Animals translocated to hunting compounds responsible for contained outbreaks in Florida and Alabama. Two human cases since 1980 associated with this variant.

Bat Rabies. Cases have been reported in 30 different species. Bat variants responsible for 15 of 18 human rabies infections acquired in the United States since 1980.

Other Wild Species. No enzootic rabies. The few dozen cases each year are spillover infections from reservoir species.

Domestic Animal Rabies. No enzootic rabies. The few hundred cases each year are spillover infections from wildlife to unvaccinated domestic animals. Control programs to maintain this low level are expensive but necessary to prevent human disease; variants transmitted by domestic dogs in areas of poor rabies control are responsible for an estimated 35,000 human deaths each year. Eleven humans rabies deaths in the United States since 1980 are attributed to these rabies variants.

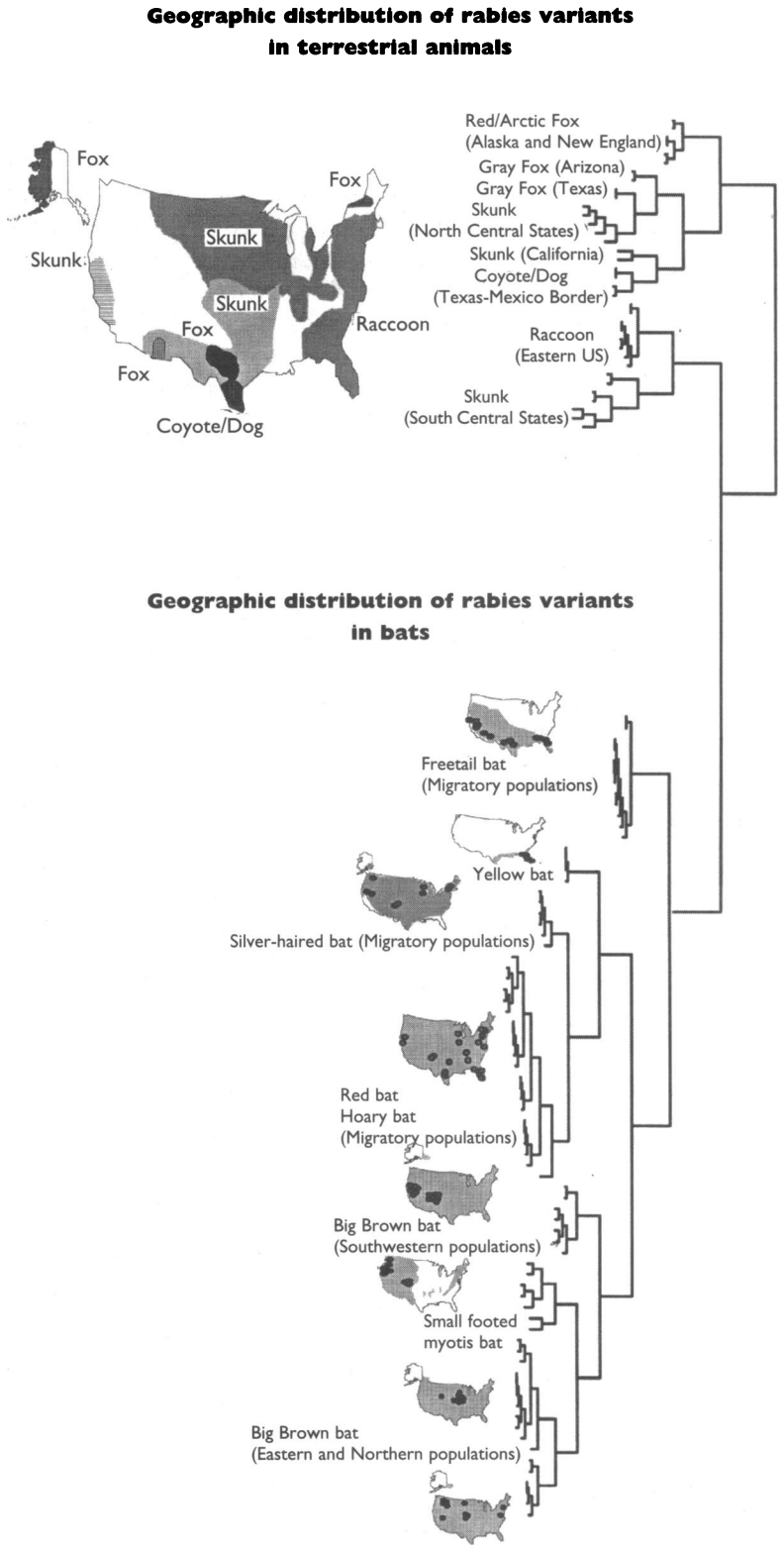


Figure 2. Genetic tree for variants of the rabies virus associated with different animal populations in the United States. This tree is based on an analysis of nucleotide differences over 320 base pairs of sequences from the nucleoprotein gene of the rabies virus. The lengths of the horizontal lines are proportional to the nucleotide difference between samples. The vertical lines are for graphic purposes only and do not suggest lineage or relationship. The bar at the base of the figure represents a branch length of 5 (that is, 5 nucleotide changes in every 100 base pairs of sequence analyzed).

Samples from related outbreaks of rabies in foxes in Alaska and New England differ by approximately 5% from each other but differ by 15% to 32% from all other terrestrial animal samples and by 22% to 27% from all bat samples.

The collection sites for isolates of rabies variants associated with particular animals map to discrete geographic areas. The boundaries for the distribution of a particular variant can be predicted, and most areas of the United States are affected by a single rabies variant transmitted by a single animal species. Because of bats' mobility, the predicted distribution of a bat rabies variant is represented by the range of a particular bat species, with the location of individual samples indicated by dots. Except for Hawaii and Alaska, all areas of the United States can expect to find several different rabies variants among rabies samples collected from bats.

nized for their ability to expose large numbers of humans, often associated with significant mortality.[21]

Finally, there are no laboratory-based studies of the comparative pathogenesis and viral shedding periods in these large-bodied canids. Thus, due to the dearth of epizootiologic, clinical, and pathogenetic information associated with rabies in wolves and their hybrids, public health officials have maintained their recommendations for euthanasia of such animals involved in human exposure, regardless of vaccination status, until additional scientific

evidence is available. This issue has been the focus of national meetings, considerable and often contentious debate, and threatened litigation. Designing similar experimental approaches and protocols to those described above for ferrets may be needed to adequately satisfy all parties.

Uncontrolled Intervention

Rabies PEP is expensive and not without risk of adverse reactions.[4] Recognition that many persons receive unnecessary PEP led to the inclusion of a public health goal calling for a 50% reduction in PEPs (from an estimated 18,000 PEPs in 1987 to 9000) by the year 2000. Typically, increases in animal rabies result in increases in the use of PEP.

In two New Jersey counties monitored before and during a raccoon rabies outbreak, PEP treatments increased more than 60-fold, from two in 1988 to 131 in 1990.[24] During this same period, reported animal rabies cases increased from 15 (all of which were in bats) to 469 (of which 460 were in terrestrial mammals).

Similarly, in New York, the estimated number of people receiving PEP increased from 84 in 1989, prior to the introduction of rabies in raccoons, to 1125 in 1992 and 2905 in 1993.[25] Reported cases of rabies in animals increased from 54 (bats only) to 2746 (2705 in animals other than bats) during this period.

In 1990, Connecticut reported 41 people receiving PEP and three reported cases of rabies in bats. Following the introduction of rabies in raccoons (the number of cases increased from 193 in 1991 to 728 in 1994), the estimated number of PEP treatments in Connecticut hospitals increased from 260 in 1991 to 887 during the first nine months of 1994.[26]

No current national estimates of PEP use are available. The available data are limited because access to human cell culture vaccines for rabies is no longer under the centralized control of state health departments, as it was in the early 1980s. In 1981 an estimated 20,000 people received PEP, while the number of reported cases of rabies in animals was 7208.[27] By 1993, the number of reported cases of animal rabies had risen 31.7% to 9495.[28]

Estimating PEP use by extrapolating from historical data and other indirect analytical methods is possible, although the accuracy of the estimates generated is uncertain and such estimates are best expressed as a range. A lower limit of 22,000 PEPs was generated by assuming that the incidence rates in 1994 were the same as in 1981 (Krebs J, Long-Marin S, Childs JE, unpublished data). An increase in animal rabies (especially raccoon rabies in densely populated areas of the mid-Atlantic and Northeast) could have resulted in more people being exposed to rabid animals and an increasing incidence of PEP. However, human population density and incidence of PEP are not always positively correlated. The upper limit of the range was generated using annual sales figures of human rabies immune globulin (HRIG) reported by manufacturers. More than 40,000 PEPs may be given annually, assuming that all HRIG was utilized and an average body weight of 125 pounds (to take into account the large proportion of children treated).

These estimates indicate that increasing numbers of humans are being treated for exposures to known or potentially rabid animals. The appropriateness of these treatments and the prevention of unwarranted PEP use requires epidemiologic evaluation of the circumstances surrounding human exposure and the adherence to approved guidelines for PEP usage.[4] Given the above estimates and a cost of $1,654[29] per PEP, the annual PEP costs for biologicals alone could now range from $36.4 million (22,000 PEPs) to $71.1 million (43,000 PEPs). This figure for the average cost per PEP is consistent with other available data. Connecticut reported costs associated with PEPs ranging from $481–$3,371 (median $1,127) for 33-pound children to $787–$4,548 for 165-pound adults (median $1,498).[26]

Public health officials must weigh the consequences of euthanizing a valued family pet against the risks of avoiding or delaying critical, albeit costly, prophylaxis.

Policy Options

Rabies PEP is primarily intended for transdermal exposure to rabies virus (a bite wound or other penetration through the skin), but a majority of the prophylactic treatments now given in the United States may be given for indirect, nonbite exposure.[30] Although nonbite routes of virus infection are possible, albeit rare, there are no documented human fatalities from indirect, nonbite exposure. In contrast, human rabies in developing countries is largely a disease of poverty and inequality of access to health care; most of the more than 35,000 human fatalities worldwide are due to rabid dog bites and lack of or inadequate PEP administration.[2] Only affluent developed countries can afford to debate many of the topics described here and to divert significant human and dollar resources to issues so relatively limited in potential public health impact. Meanwhile, the global problems of rabies await redress.

It is extremely unlikely that any future policy decisions will significantly lower this country's rabies-related human mortality, which is already rare. In one sense this is unfortu-

nate: the danger lies in using this rarity as a rationale for discontinuing support for the very infrastructure that has so reduced rabies deaths. Lowering program expenditures would likely have a seriously deleterious effect on the integrated local, state, Federal, and international expertise needed for modern rabies surveillance, prevention, and control. We must continue to identify the ecological factors contributing to the emergence of rabies during the past half century to prevent its recurrence while developing sensible, cost-effective methods to effectively deal with this fatal disease.

Advances in technology may lead to the development of faster, more sensitive, and more specific diagnostic procedures as well as less expensive PEP methods. Applied research on the epidemiology of human rabies PEP could provide basic data on the appropriateness of current treatments in the light of realistic risk assessments and help redefine the treatment practices of primary caregivers.

Finally, it will be crucial in the next century to separate confusing societal conundrums—such as the appropriateness of animal ownership and the way people interact with the environment—from infectious disease management.

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