RABIES REDUX: A REVIEW OF RABIES AND OTHER CRITICAL WILDLIFE ZOONOSES

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WILDLIFE AND ZOONOTIC DISEASES

Zoonoses, infectious diseases that are transmissible from animals to people, are among the most important animal and public health problems affecting the well-being of societies worldwide. Recent analyses estimate that about 60% of all infectious disease agents affecting humans are zoonotic in origin and that 75% of emerging infectious diseases of humans are zoonotic.[1] Free-ranging wildlife have been an important source of zoonotic infections throughout history and are implicated in most emerging zoonoses. A possible outbreak of bubonic plague transmitted by wild rodents and caused by the bacterium *Yersinia pestis* was described in the Old Testament in the First Book of Samuel. Similarly, rabies transmitted by a suite of wild animals can be traced back to Chinese, Egyptian, Greek, and Roman records. Wildlife were involved in the recent emergence of important human diseases such as Ebola hemorrhagic fever and highly pathogenic H5N1 avian influenza virus and likely will be important in yet undiscovered and undescribed zoonoses.

RABIES

Etiology

Rabies has been described as the oldest zoonosis in the world. It is caused by a nonsegmented, negative-stranded RNA virus in the Family *Rhabdoviridae* and genus *Lyssavirus*. Other *Lyssavirus'* include Lagos bat virus, Mokola virus, Duvenhage, Australian bat lyssavirus, and European bat virus 1 & 2. Rabies has a near cosmopolitan distribution. Antarctica and Australia are the only rabies-free continents, although several isolated rabies-free countries do exist.

Pathogenesis

All mammals are believed to be susceptible to rabies. Rabies transmission usually begins with the bite of an infected host, although transmission has been documented via mucous membrane contamination, aerosol transmission, and corneal and organ transplants. The inoculated virus then enters peripheral nerves directly or replicates in non-nervous tissue prior to neuronal entry. Retrograde axoplasmic flow transports virus from the peripheral to the central nervous system where viral dissemination is rapid. Classic behavioral changes are associated with active cerebral infection. The virus then passively spreads centrifugally to highly innervated tissue like salivary glands and the cycle is repeated. Rabies infection in unvaccinated humans considered uniformly fatal, although a few cases of people surviving confirmed rabies infection have been reported worldwide. In domestic and wild animals, rabies also is thought to be uniformly fatal, although this might not be the case with some bats where persistent sub-clinical infections could be more common than once thought.

Wildlife Reservoirs in the United States

Within the United States, wild animals accounted for 93% of the reported rabies cases during 1997.[2] In the United States, rabies in terrestrial wildlife occurs in spatially defined areas where they generally have a defined wildlife reservoir, in part because an infected wildlife species is most likely to infect a conspecific. For example, a rabid raccoon (*Procyon lotor*) is most likely to encounter and infect another raccoon or a rabid skunk (*Mephitis mephitis*) is more likely to encounter and infect another skunk. Because rabies is a RNA virus, which are prone to mutation, distinct rabies virus variants eventually emerge giving the rabies variant and distribution patterns currently seen in wildlife species. Rabies variants can be distinguished antigenically with panels of monoclonal antibodies or by comparing patterns of nucleotide substitution. Currently a raccoon rabies variant is enzootic in all of the eastern coastal states as well as Alabama, Ohio, Pennsylvania, Tennessee, Vermont and West Virginia. Three distinct skunk (primarily *Mephitis mephitis*) variants occur in California, north central US and south central US. In Alaska, fox rabies occurs in red foxes (*Vulpes vulpes*) and arctic foxes (*Alopex lagopus*). Fox rabies also is present in gray foxes (*Urocyon cinereoargenteus*) in parts of Arizona and Texas. Rabies also exists in Puerto Rico where the defined wildlife reservoir is the slender mongoose (*Herpesetes javanicus*).

Due to their mobility, defined areas of bat rabies do not occur as is seen with terrestrial rabies and bat species known to be rabies reservoirs can be found throughout the continental United States (not in Hawaii). Distinct bat variants do occur and are associated with different species of insectivorous bats in the United States. Transmission of rabies from bats to terrestrial mammals does occur, but rarely results in sustained, independent transmission in the infected non-bat species. An exception to this was the 2001 adaptation of a big brown bat (*Eptesicus fuscus*) rabies variant to skunks in Flagstaff, Arizona. In this area, which previously was free of terrestrial rabies, the big brown bat virus variant now circulates within and has become adapted to striped skunks.

Wildlife Reservoirs Outside of the United States

In many countries other than the United States, domestic dogs often are reservoirs for rabies virus. The virus also can circulate in a defined wildlife reservoir within a spatially defined area. For example, the yellow mongoose (*Cynictis penicillata*) is considered a rabies reservoir in South Africa and jackals (*Canis* spp, mostly *C. mesomelas*) are considered a rabies reservoir in parts of Namibia, Botswana, Zimbabwe, and South Africa.[3] This suggests that the transmission and adaptation of domestic dog rabies variants to local wildlife host species seen in the United States also occurs elsewhere

in the world. Interestingly, an outbreak of rabies in greater kudu antelope (*Tragelaphus strepsiceros*) that was estimated to have killed 30,000 to 50,000 animals is believed to have originated from rabid jackals but perpetuated via oral transmission of the virus from kudu to kudu.[3] Although the epizootic did not result in the development of a defined wildlife host, this demonstrates that nontraditional transmission can occur in wildlife populations.

Rabies Exposure in People

In the United States, bat-associated rabies variants account for the majority of human rabies infections in recent years. Common bat-associated rabies variants infecting humans in the United States include one normally associated with the Eastern pipistrelle (*Pipistrellus subflavus*) and the silver-haired (*Lasionycteris noctivagans*) bats and another associated with the Mexican free-tailed bat (*Tadarida brasiliensis*). Interestingly, most human cases of bat-associated rabies do not report a known history of a bat bite and some do not even report exposure to a bat. Although it can occur, domestic dogs and cats are not commonly infected with bat-associated rabies variants but are more often infected with regional terrestrial rabies variants. This does not mean that one should dismiss the potential for rabies exposure when domestic dogs or cats come in contact with bats. Regardless, vaccination of domestic dogs and cats against rabies is essential for protecting humans against rabies.

Rabies Control

Despite a documented history of rabies transmission from wildlife to humans, the use of population-reduction or wildlife culling programs to control rabies is undesirable. In the United States, the greatest reduction in transmission of rabies from wildlife to humans has come from the vaccination of domestic animals, especially dogs and to a lesser extent cats. Widespread vaccination of domestic dogs in the 1940s and 1950s eliminated the circulation of major canine rabies variants and reduced the transmission of wildlife variants to humans by eliminating the major link between humans and wildlife, domestic dogs and cats infected by a terrestrial wildlife rabies variant who then bite and infect humans.

Annually, the National Association of State Public Health Veterinarians publishes the Compendium of Animal Rabies Prevention and Control in the Journal of the American Veterinary Medical Association. This details recommendations that serve as a basis for animal rabies prevention and control in the United States. While this does not supersede state and local laws or requirements, it is the basis for instituting an effective national rabies control program and should be read annually by all veterinarians in private or public practice.

Distribution of an oral rabies vaccine has been used to control, and in some instances eliminate rabies in terrestrial wildlife and at times it can be an important adjunct to traditional rabies control methods. The oral rabies vaccine (V-RG) is a vaccinia-rabies glycoprotein recombinant virus vaccine in which the gene for the rabies G-protein has been inserted into the vaccinia virus TK-gene. The percent of target wildlife population needed to be vaccinated depends on susceptible population density, bait uptake and vaccine efficacy in the target wildlife species. Efficacy is species-specific. More than 80% of field-vaccinated raccoons survived a severe laboratory rabies challenge but the vaccine does not effectively vaccinate skunks. The vaccine is currently only licensed for raccoons and coyotes (*Canis latrans*). Oral rabies vaccination successfully eliminated a canine rabies virus variant maintained in coyotes in south Texas and also is believed to have reduced a gray fox rabies variant in west and central Texas. The oral rabies vaccine is not available to private veterinary practitioners for private or commercial use. The primary role that practicing veterinarians play in controlling rabies is through the vaccination of domestic animals using approved vaccines as licensed in the United States and educating the general public about the risk of rabies exposure as it relates to domestic animals and wildlife.

BARTONELLA

Etiology and Disease

Bartonella species are short, pleomorphic, gram-negative rod-shaped bacteria in the family Bartonellaceae that have recently been identified in a wide range of domestic and wild mammals. Previously characterized as *Rochalimaea* species, the advent of new molecular tools, such as polymerase chain reaction assay, revolutionized our understanding of and ability to detect and differentiate new *Bartonella* species. It is unclear if all novel *Bartonella* species identified are zoonotic. *Bartonella* spp are usually vector borne. *Bartonella henselae* is the etiologic agent of cat scratch disease in humans and *B. quintana* and *B. henselae* (mainly) are known to cause endocarditis in humans. *Bartonella* spp also can cause bacillary angiomatosis in immunocompromised people. Due to the high prevalence of *B. henselae* infection in cats, it is difficult to associate infection with disease, but experimental infection suggests it can cause fever, local inflammation at the site of inoculation, lymphadenopathy, lethargy, anorexia, and occasionally central nervous system disorders and reproductive disorders. The clinical spectrum of *B. vinsonii* subspecies *berkhoffii* in dogs is expanding and includes endocarditis, arrhythmias, myocarditis, granulomatous lymphadenitis, and granulomatous rhinitis as well as possibly polyarthritis, neutrophilic or granulomatous meningoencephalitis, immune-mediated anemia, thrombocytopenia, and eosinophilia. As with cat and *B. henseleae*, *B. vinsonii* subspecies *berkhoffii* also has been isolated from clinically healthy dogs, which could be long-term carriers of the bacterium.

Domestic and Wildlife Reservoirs

Four species have been isolated from domestic cats, which appear to be the main reservoir for at least three *Bartonella* species: *B. henselae*, *B. clarridgeiae*, and *B. koehlerae*. Multiple *Bartonella* species have been isolated from domestic dogs, but are not considered to be reservoir hosts for any *Bartonella* species. Domestic cattle are reservoirs of *B. bovis* and *B. chomelii*. Wildlife species are reservoirs for most other Bartonella species in the US and Canada (Table 1).[4] Interestingly, *B. henselae* DNA also was isolated from two harbor porpoises (*Phocoena phocoena*) but the geographic distribution and mode of transmission in harbor porpoise is currently unknown.[5]

THE ROLE OF VETERINARIANS IN CONTROLLING ZOONOSES

Prevention and control strategies for zoonoses like rabies and *Bartonella* spp must take wildlife and their epidemiological role into account. Veterinarians play an important role in diagnosing these diseases in domestic animals, preventing their transmission through appropriate vaccination and vector control and educating the public about risk. Veterinarians also can play an important role by educating the public about and helping to prevent the human movement of wildlife. Anthropogenic movement of wildlife infected with zoonotic agents has been responsible for the translocation of zoonotic agents and epizootics in wildlife, such as the late 1970s mid-Atlantic translocation of infected raccoons from the Southeast into the mid-Atlantic United States.

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Table 1. Known North American *Bartonella* Species, Wildlife Reservoir, and Zoonotic Status (Adapted from Chomel et al, 2004)[4]

Bartonella species	**Wildlife Reservoir**	**Vector or Potential Vector**	**Zoonotic Status**
B. elizabethae	Rats (*Rattus norvegicus*)	Unknown	No
B. peromysci	Field mice (*Peromyscus* spp.)	Unknown	No
B. species unknown	Prarie dogs (cynomys ludovicianus)	Fleas?	No
B. tribocorum	Rats (*Rattus norvegicus*)	Unknown	No
B. vinsonii arupensis	White-fooded mice (*Peromyscus leucopus*)	Fleas? Ticks?	Yes
B. vinsonii berkhoffii	Coyotes (*Canis latrans*)	Ticks?	Yes
B. vinsonii vinsonii	Meadow voles (*Microcus pennsylvanicus*)	Ear mites?	No
B. washoensis	Ground squirrels (*Spermophilus beecheyi*)	Fleas? Ticks?	Yes