Although rabies has been almost completely eradicated from domestic animal populations around the world, its recent reemergence in wildlife over the past several decades may be cause for alarm. The estimated cost spent on the control of rabies in the United States may exceed 1 million dollars per 100,000 people (domestic animal vaccinations included) (Acha 2003). Even though there are still very few human cases in the United States, nearly 50,000 people die from rabies every year, worldwide (Strauss and Strauss 2002). Rabies mortalities across the globe outrank yellow fever, polio, and meningococcal meningitis. Mostly, people affected are in poor, developing countries where vaccinations are not required for domestic animals or are simply too expensive to obtain. In India alone, 30,000 cases of human rabies are reported every year (Plotkin 2000), and post-exposure vaccinations for just one person can cost up to $2,200 (Baer 1998). Although skunks, raccoons, foxes, and other such terrestrial mammals currently make up the majority of reservoirs, bats may pose the greatest threat in the future (Plotkin 2000).

Rabies first appeared in recorded history around 4,000 years ago in the pre-Mosaic Eshnunna Code of Mesopotamia, and it has been written about often in the centuries that followed. Although no one at the time understood its etiology, early writers such as Aristotle and Democritus seem to have been quite proficient at diagnosing rabies; however, effective treatments throughout history have been practically nonexistent (Rosner 1974). During the nineteenth century alone, approximately 100 different chemical agents were used in attempts to treat rabies, not including the plethora of physical treatments such as bloodletting, cauterization, and amputation. Towards the latter portion of the nineteenth century, most physicians were convinced that if any treatment succeeded in curing rabies, it was only substantial proof of misdiagnosis. This era of frailty paved the way for Louis Pasteur to make the first truly scientific attempt at stoping the development of rabies. From 1885 to 1895, his work with rabies is mentioned nearly one hundred times in *The Lancet,* and his discovery of the first vaccine is one reason why he is now known as the father of immunology (Carter 1982).

Unfortunately, over a hundred years later, rabies is still one of only a few human diseases boasting a near 100% mortality rate (Whitley and Gnann 2002). Typically, the incubation period of rabies in humans is 20-60 days. That is an average based on the majority of cases; however, symptoms can occur within 5-6 days or as long as 6 months, as in 1-3% of reported cases. The long incubation period is somewhat part of the terror this disease has caused throughout the ages, as it seemingly flares up spontaneously in some individuals not connecting the illness to contact with a rabid animal. The virus affects the central nervous system (CNS), and symptoms range from hyperactivity to paralysis. Within 2-12 days after symptomatic onset, the patient begins to slip into a coma, and cardiorespiratory failure is almost always the eventual cause of death (Plotkin 2000).

Since World War II, there have been three major rabies epidemics in the wildlife populations of industrialized countries. One involved the red fox (*Vulpes vulpes*) in Europe; another involved raccoons in the eastern United States; the third involved the arctic fox (*Alopex lagopus*) in Canada (Real 2005). Although each of these outbreaks has sparked a great deal of interest in the medical community, a new rabies epidemic may be on the horizon. Even though bat-related rabies has been observed for hundreds of years, its escalating prevalence since the 1950s may be cause for alarm (Kunz and Fenton 2003).

Between 600 and 1,000 cases of bat rabies have been reported in the United States every year since 1980. Bat-related rabies, however, is not a recent phenomenon (Rupprecht *et al.* 1996). Of the seven genotypes of *Lyssavirus,* six have been found in bats. This leads some scientists to believe that bats were the original reservoir for rabies and that it crossed over to canines and other animals from them (Plotkin 2000). Genotype one is commonly referred to as the classic rabies virus, and the other six genotypes are as follows: Logos bat virus (genotype two), Mokola virus (genotype three), Duvenhage virus (genotype four), European bat lyssavirus type one (genotype 5), European bat lyssavirus type two (genotype six), and Australian bat lyssavirus (genotype 7). Mokola virus is the only genotype not known to be present in bat populations. In addition to these listed previously, four other viruses in southeast Asia have also been considered to be part of the lyssavirus genotypes, but no research has yet unearthed conclusive evidence (Davis *et al.* 2005).

A recent study has shed new light on the origin of the classic rabies virus and given insight into the history of rabies' evolution. They studied 55 isolated strains of rabies from around the world, 36 of which were found in animals belonging to the Carnivora orders (terrestrial mammals such as wolves, raccoons, skunks, cats, and dogs) and 17 in members of order Chiroptera (bats). The remaining two strains are associated with the Mokola virus, but the organisms that spread this pathogen are currently unknown. Their research has clearly shown that point mutation and purifying selection are the two driving forces in the evolution of all lyssaviruses. They suggest that chiropteran lyssaviruses were present long before the appearance of what is commonly called the classic rabies strain. The classic virus, a derivative of serotype one, mutated and split away form bat populations thousands of years ago. Their report suggests that movement of lyssaviruses between chiropteran and carnivoran hosts has occurred many times throughout history and still occurs today (Badrane and Tordo 2001).

The northern Arizona skunk population was known to be devoid of rabies for many years until a dead skunk was found in Flagstaff in 2001. Tissue samples were delivered to the Arizona State Health Laboratory, and the animal was diagnosed with bat-related rabies. Over the next few months, 18 more skunks were found either dead or behaving strangely and were reported in similar fashion. To date, this is the largest recorded number of terrestrial mammals contracting bat lyssavirus in such a short period of time. Clearly, bat lyssavirus has the ability to manifest itself in skunk populations and is still moving between species (Leslie *et al.* 2006). Skunks, regrettably, are not the only animals that research has found vulnerable to bat-related rabies. In Europe, where bat lyssavirus is particularly rampant, a stone marten (*Martes foina*) was killed by a German citizen in 2001. The animal was suspected rabid, and further testing revealed that bat lyssavirus type one was the cause (Muller *et al.* 2004). Additional cases of bat lyssavirus have also been diagnosed in European sheep as well. This turn of events may be cause for concern because bats are not as easily vaccinated as terrestrial mammals (Pounder 2003).

In Europe, the red fox (*Vulpes vulpe*) is the primary distributor of rabies. Large-scale oral vaccinations over the past 25 years have nearly eradicated the disease from many parts of Europe (Vos *et al.* 2004). In North America, similar actions have been taken to combat the ever-growing threat of raccoon and skunk rabies (Finnegan *et al.* 2002). Both programs seem to have positive results, but the question remains: if a strain of rabies persists in the bat populations of both continents that is transmittable to the resident terrestrial mammals, how can health authorities ever hope to fully wipe out the disease? Currently, there is little or no information on how to effectively vaccinate bat populations with any true efficacy. Because bats hunt by echolocation, as opposed to the scavenging technique of foxes, skunks, and raccoons, it is extremely unlikely that a cost-effective mode of oral vaccination will be developed (Kunz and Fenton 2003). Obviously, it will be of no avail to rid the terrestrial mammal populations of rabies if they can invariably be re-infected by strains of bat lyssavirus.

Wild animals are not the only animals affected by bat-related rabies. Every year, more than one million cattle die in Latin America because of the disease. Most of these episodes are due to the bite of *Desmodus rotundus*, the vampire bat (Martinez-Burnes *et al.* 1997). Vampire bats were first observed to transmit lethal strains of rabies to domestic animals as early as the 1500s. They are particularly threatening because they sometimes serve as carriers while still functioning in perfect health (Malaga-Alba 1954).

Although a substantial amount of research has been conducted on rabies in general, many questions still remain. One such question, if unanswered, may be the root of problems in the future. Although it is widely understood that when the virus enters the body it is considered to be cell-free, no one is completely certain where the virus resides during the latent period before invading the CNS months later (Plotkin 2000). This mystery has led many researchers to question how a virus that so quickly kills its hosts can survive for thousands of years. The asymptomatic latent period is most likely what enables the virus to continue spreading. Five different cases of human rabies were documented to have experienced an incubation period of seven years or more (Strauss and Strauss 2002). Granted that humans tend to be quite resistant to rabies having a 40% infection rate and an uncommonly long incubation period, most terrestrial mammals tend to die much sooner and much more easily (Aitken and Jeffries 2001). Bats, on the other hand, are the only other mammal known to have a substantially long incubation period, resisting the virus and prolonging death (Strauss and Strauss 2002).

Although bats are not usually the primary source of infection throughout the world, they do pose the most significant threat to the individual person. 21 cases of human rabies were attributed to bats in the United States between 1980 and 1996 by way of nucleic acid analysis. What is so startling about these case studies is that only one of these patients had a firmly grounded history of a bat bite. Because of the relatively small size of Chiropteran teeth, in the event of a bat encounter, many people do not realize they were bitten or that their experience was anything like an attack. Although a very small number of bats captured and tested in the United States are found to be rabid (< 1 %), in the state of Colorado, 30% of bats who actually bit people and 50% of those that were found in houses were carrying rabies. In light of this new research, the Advisory Committee on Immunization Practices has issued a new warning about rabies vaccination that encourages people who have had any contact or even possible contact (since many bats bite people in their sleep) with bats to seek immediate medical attention (Plotkin 2000).

In recent years, a new phenomenon has occurred involving the aerosol transmission of bat lyssavirus**.** This has typically occurred in bat caves where spelunkers or researchers have inhaled the fumes of ageing bat guano and saliva. There are also cases of lab-workers developing the disease by unintentionally breathing in fumes of viral aerosol particles (Plotkin 2000). Experiments conducted in the late 1970s illustrated that some animals easily contract rabies intranasally, and others seem to be immune to that mode of incidence. Skunks were one species found to always develop onset of symptoms when rabies virus was introduced into the nasal passages**.** Actual contraction of the disease is thought to be through the mucous glands (Charlton and Casey 1979b). A replica experiment was conducted by the same researchers on mice and found that intranasal introduction of virus rarely resulted in development of disease. Obviously, an organism's susceptibility to developing rabies intranasally varies greatly by species. Regardless, research does support the idea that animals and even people can develop rabies by aerosol means, and this would likely occur in and around bat-inhabited caves or barns due to the high concentration of viral particles found in the buildup of guano and saliva. Aerosol transmission may similarly play a large role in the development of rabies in bats, but further research is needed to confirm whether or not this actually occurs (Charlton and Casey 1979a).

One reason bat-inhabited caves may pose such a threat in the spread of rabies is that bats are communal animals, naturally occurring in high population densities. This allows any infectious disease to easily spread from one member of the community to another. In some cases, even different species of bats have been observed to share the same caves, permitting diseases to adapt and evolve the capacity to move between species. There have even been numerous accounts of rabid bats of one species attacking bats of other species, possibly transmitting rabies in the mix (Kunz and Fenton 2003). Also, some preliminary work in the 1950s revealed that hibernating bats play a role in helping diseases like Japanese B encephalitis overwinter, but whether rabies is one such pathogen has yet to be determined (La Motte 1958).

Flight is also an obvious feature that facilitates the spread of communicable disease. The ability to fly allows for quick dissemination of viral pathogens, particularly in the migratory bat species (Kunz and Fenton 2003). Although rabies is a worldwide epidemic, there are parts of the world in which no traces of the virus have been observed. Jamaica, Uruguay, Japan, Ireland, the Netherlands, and even Hawaii are just a few. All of these land masses are surrounded by water on at least three sides. If rabies does move naturally into these unaffected areas, it is more likely to be by migratory bats than by terrestrial mammals (Acha 2003).

The United Kingdom, for example, was once thought to be completely devoid of rabies after vaccinations wiped out the virus in the early twentieth century (Acha 2003). In 2002, however, a United Kingdom bat conservationist died after suffering from a bat bite. Although 20 people were recorded to have died of rabies since the 1920s when it was allegedly eradicated, all of them contracted the disease from outside the U.K. This 2002 episode was the first incidence of its kind since 1902. The virus that killed the conservationist was closely related to the negative stranded RNA virus known as European bat lyssavirus type two. It has resulted in four human deaths in Europe since 1977 and two human deaths in Australia since 1996. Typically, European bat lyssavirus has been detected in two species of bats in mainland Europe: lyssavirus type one in Serotine bats (*Eptesicus serotinus*) and type two in Daubenton's bats (*Myotis daubentonii*). Somehow the disease made its way across the English Channel. After researchers studied 2,000 different U.K. bats over a period of 15 years, only two bats were found to be infected, both of which were *M. daubentonii*. Normally, human contact with *M. daubentonii* is extremely unusual. This particular species does not naturally roost in areas where the public may be active, however, there are species that do. Members of genus *Pipistrellus* and the long eared bats, *Plecotus auritus*, commonly roost in British homes. Although European bat lyssavirus has not yet been observed to exist in the more common bats, studies have shown that it can be passed between species (Pounder 2003). One can infer that the more common species of bats could easily be affected by lyssavirus if given the opportunity. The appearance of such rabid species may only be a matter of time. If this were to occur, the limited areas of human risk to bat lyssavirus would greatly expand. Currently, only those working with wild bats on a regular basis (conservationists, researchers, graduate students) are at any genuine risk. People in these fields should be vaccinated for rabies regardless of whether or not it is known to occur in the species they are studying. Conversely, if the disease should become more widespread throughout the community of bat species, the area of human risk will expand as well. The question persists: what can be done to prevent the outbreak of European bat lyssavirus should it move to infect the more commonly occurring species? Bat lyssavirus is no different from classic rabies, malaria, bubonic plague, or any other zoonotic pathogen. The only way to contract the disease is through direct contact with an infected animal, in this case, *M. daubentonii*. Reason implies that in order to make an effective assessment of the disease, researchers must first track and study its source. A Geographic Information System in Costa Rica has already paved the way for such research to be done (Badilla *et al.* 2003).

In September of 2001, the National Children's Hospital in Costa Rica reported a possible case of rabies in a young child. Prior to this report, the last officially documented case was in 1970. Supposedly, the 70s witnessed a period of control over the disease, particularly in domestic animals. As in the U.K. and mainland Europe, people in Costa Rica thought the terror of rabies had finally come to an end. As time moved on, however, reports of rabies began to surface again. The first occurrence was a report of canine rabies in 1987, and not long after, 26 cases of rabies emerged in cattle. These events culminated on September 29, 2001, when a nine-year-old boy died of the virus in the National Children's Hospital. Follow-up research was conducted, and investigators discovered that the boy, along with his 62-year-old caretaker, died of rabies acquired from a pet cat. The cat, however, had contracted the disease from a vampire bat of species *Desmodus rotundus* (Badilla *et al.* 2003). This species of vampire bat is also held responsible for an outbreak of human aggression in Brazil that occurred in the early 90s and left 308 people infected with rabies (Goncalves *et al.* 2002). This recent reemergence of rabies in Costa Rica combined with the recent cases worldwide has reinforced the need for work that began in Costa Rica in the early 80s. The Program of Animal Health of the *Ministerio de Agricultura y Ganaderia* implemented a Geographic Information System to help deal with the possibility of rabies infestation. This plan of action divides the country into 2,234 areas of study, each 25 square km in size. Veterinary technicians utilized data from a national census of animals and obtained various frequencies of vampire bat bites in domestic animals as well as the presence or absence of rabies virus in various bat populations across the countryside. These figures combined with a number of ecological dynamics such as temperature, precipitation, altitude, and human inhabitation of land area helped define each of the 25 square km districts as either low, medium, or high-risk areas for rabies virus (Badilla *et al.* 2003).

The reemergence of rabies in areas around the world is not yet cause for public panic, but it is cause for alarm. If an outbreak was to occur for any number of reasons, Costa Rica's Geographic Information System could easily serve as a guide for authoritative action. Citizens living in high-risk areas could be notified, watched, and in worst case scenario, even quarantined. Some states in the U.S. have similar tracking systems for raccoon and skunk populations, but the growing threat of bat lyssavirus elicits a need for systems that track bat populations as well. Due to the complex nature of widespread, wildlife vaccinations, a Geographic Information System is the best way to assist health authorities in keeping track of where the rabies virus is most likely to spread. If bat rabies, or any other type for that matter, were to suddenly invade the borders of a state or country, areas at greatest risk for infiltration could be identified, and animal control personnel could easily implement whatever system of response is in their protocol in those areas. This would cut back on the waste of precious time and money in the state of an emergency (Curtis 1999).

Byproducts of such a tracking system would have more positive effects than just the prevention of rabies outbreaks. Because bats carry so many different viral infections, many of which are spread in similar fashion as rabies, the proposed system would help in the prevention of those diseases as well (Kunz and Fenton 2003).

From fall of 1998 to spring of 1999, an outbreak in Malaysia of what is now called Nipah virus took the lives of 105 people and led to the slaughter of more than one million domestic pigs. This was the first reported occurrence of such a disease, although it does have links to the Hendra virus in neighboring Australia. Hendra virus is typically carried by pteropid bats (flying foxes), and similar species were targeted for the preliminary research on Nipah virus. 324 animals representing 14 species of bats were sampled. 21 bats from five species (*Pteropus hypomelanus, P. vampyrus, Eonycteris spelaea, Cynopterus brachyotis*, and *Scotophilus kuhli*) were found to have neutralizing antibodies for Nipah virus and are now known to be reservoirs of the emerging disease (Johara *et al.* 2001). In addition to these new diseases, West Nile virus has also been witnessed in a small number of bats around the world, although research shows them to be unlikely hosts on a large scale (Davis *et al.* 2005). Even histoplasmosis has been found in association with bat-inhabited caves in recent years (Lyon *et al.* 2004). Countries that possess a working Geographic Information System for bat populations will also have a good head start on these diseases because the approach is host-specific and not disease-oriented (Curtis 1999).

Although rabies does not exist in human populations on a scale that could be considered truly epidemic, it is a problem that has persisted for thousands of years and almost certainly will continue far into the future. Likely, it has always been widespread throughout wild populations around the world, only becoming visible after the worldwide vaccination of domestic animals in the early twentieth century. Although bats are not currently the primary candidate for the worldwide spread of rabies, their covert infiltration of human populations and their imperceptible modes of transmission make them a terrible threat for present and future generations (Kunz and Fenton 2003). Given that no cure for post-symptomatic rabies has yet been discovered, the vaccination of wildlife populations combined with reservoir tracking systems and innovative methods for assessing areas at highest risk for transmission are mankind’s greatest defense against this ever-changing disease.

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