Rabies Update for Travel Medicine Advisors

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Rabies is a neglected disease in many developing countries. It is preventable, and the tools to prevent it are known. There is urgent need for more funding, for study of innovative dog population–control measures, and for sustainable canine immunization. Safe and effective tissue-culture rabies vaccines and human and equine rabies immunoglobulins (HRIG and ERIG) are not readily available in many regions where rabies is endemic. This and the continuing presence and spread of rabies have increased the risk for travelers, who cannot rely on being able to receive optimal postexposure treatment in many parts of the world. Alternatives to HRIG or ERIG are not available. Travelers who leave the safe environments of tourist hotels and buses in regions of Asia, Russia, Africa, and Latin America where canine rabies is endemic may be at risk of life-threatening exposure to rabies.

Rabies, the infectious disease with the highest known case-fatality rate, remains a worldwide threat. More humans die of rabies than die of Japanese encephalitis, leprosy, and polio [1, 2]. Rabies is not notifiable in many countries, making prevalence statistics unreliable. Global estimates indicate that there are ∼50,000 annual human deaths [3]. In Asia, Africa, Russia, parts of South and Latin America, and most of the newly independent former Soviet republics, dogs are the primary vector of rabies. Dogs, as well as wildlife, are responsible for rabies transmission in most of Africa. A few hundred rabid dogs and cats are reported every year in North America and Europe, but they are usually infected with “spillover” rabies virus that circulates among wildlife prevalent in that region [4]. In Latin American countries, government-supported canine vaccination and control programs have dramatically reduced the incidence of rabies in dogs; however, insectivorous and vampire bats continue to expose humans and animals. Efforts to replace dangerous and poorly immunogenic nerve tissue–derived (Semple and suckling mouse brain) products with inactivated tissue-culture rabies vaccines have been particularly successful in Southeast Asia and Sri Lanka. Rabies vaccines that are produced in primary hamster kidney cells are manufactured in China and Russia, but these are not yet on the World Health Organization (WHO) recommended list [3]. Many countries with large populations of stray dogs are popular tourist destinations. Unvaccinated dogs outnumber vaccinated ones in countries where canine rabies is endemic, largely because of the lack of adequate funding and because of logistic factors [2, 3].

In the emergency department of one Thai teaching hospital, animal bites represented 5%–6% of all admissions in 1990–1991 [5]. Approximately 40% of reported dog bites worldwide occur in children, and the majority occur on the face, neck, and head [5, 6]. Receipt of severe, multiple bites—and, particularly, bites on the face—is associated with shorter incubation periods and a higher risk of developing rabies [6–9]. In Asia, which reports the most rabies-related deaths, ∼40% of deaths involve children aged ≤15 years. The offending dog is usually not available for examination, and there are few local animal quarantine facilities and reliable diagnostic laboratories. Thus, most postexposure prophylactic (PEP) treatment is rendered without knowledge as to whether the biting animal was indeed rabid. Dog bites represent a huge financial burden to governments that must mandate PEP treatment for animal-bite recipients. Physicians dealing with travel medicine cannot ignore rabies, and several reviews have been published recently [2, 10, 11]. This essay attempts to address only the most pressing rabies problems that may confront travelers today.

Travelers should be aware that appropriate PEP treatment...
might not be readily available in much of Asia, Latin America, and Africa. More importantly, nerve tissue–derived rabies vaccines of unreliable potency and high rates of associated complications are still being used [12, 13]. Neurological complications associated with Semple (sheep brain–derived) vaccine may be as high as 1 case per 200 recipients, and, in one African country, the locally produced product contained residual live virus [13]. Imported tissue-culture rabies vaccines are expensive and are not locally available. They are generally only available in the large urban centers of Asia, Africa, and parts of Latin America [10, 14, 15]. Human diploid cell vaccine (HDCV), the most expensive product, has been replaced in many countries by less costly tissue-culture rabies vaccines, such as purified Vero cell vaccine (PVRV; Aventis) and purified chick embryo cell vaccine (PCECV; Chiron). These are as safe and effective as HDCV [3, 10]. Two economical reduced-dose intradermal regimens of tissue-culture rabies vaccine recommended by the WHO have been used since 1988. They are up to 75% less expensive than the intramuscular regimen and are as safe and effective [14–16]. Intradermal PEP treatment is actually more cost-effective than are nerve tissue–derived products if indirect costs are considered [14–16].

Visitors to countries where canine rabies is endemic must assume that most local dogs have not been vaccinated. Although excellent, inexpensive veterinary rabies vaccines (US$0.35–US$0.50 per dose in Thailand) are available, mass vaccination of dogs is not effective in most of Asia and Africa. In some countries, control of the dog population is almost impossible to implement because of cultural and religious beliefs and because some animal welfare organizations have hindered humane efforts to control the canine population. There is a lack of motivation and funding by governments to develop sustainable canine population control and vaccination programs. Oral attenuated and recombinant rabies vaccines have virtually eliminated fox rabies in western Europe, and similar programs are being applied in North America that target raccoon and fox rabies. In Asia, such oral vaccines may be one tool for controlling rabies in stray dogs and cats [17–19].

Diagnostic facilities for rabies in Asia and Africa are limited, but they do exist in parts of India, The Philippines, Latin America, Russia, Sri Lanka, and Thailand. However, patients with rabies usually receive diagnoses on clinical grounds. Affected persons are often sent home to die, because there is no effective treatment, and most hospitals avoid admitting persons with rabies. Molecular technology can improve clinical diagnosis and our understanding of pathophysiology, epidemiology, and the dynamics of interspecies transmission [2, 20, 21]. This may enable us to design more-effective rabies-control strategies.

Optimal PEP treatment includes immediate wound washing with copious amounts of water and an antiseptic, such as povidone-iodine or alcohol. This is followed by the use of human or equine rabies immunoglobulin (HRIG or ERIG) for all transdermal wounds and a WHO-approved vaccination series. Rabies immunoglobulin (RIG) must be injected into and around wounds to neutralize virus before it enters peripheral nerves, where, once established, it is in an immune-protected environment [2, 10, 22, 23]. In cases of severe exposure, RIG should be administered on the first day of treatment but not later than 7 days after the start of a vaccination series, when it may suppress the endogenous immune response [24]. Vaccine requires ~7–10 days to induce detectable neutralizing antibodies [22, 24, 25].

Short incubation periods for rabies have been reported, as have occasional true PEP treatment failures (i.e., deaths that occur when optimal treatment was rendered) [23]. Deaths have also been reported due to “management errors.” These are usually the result of a delay in treatment, the lack of RIG administration, or the failure to inject RIG into all bite wounds [2, 10, 22, 23]. RIG and even tissue-culture vaccines are often in very short supply or unavailable. A patient may receive only vaccine and will have to travel elsewhere to obtain RIG, causing delay, added risk, and unplanned expenses. One reason for the short supply of ERIG and HRIG involves the ever-increasing manufacturing requirements that increase production costs. Because these products are not profitable, many international firms have discontinued production [26, 27]. For example, a new imported ERIG that meets the latest European Pharmacopoeia standards is ~20%–30% more expensive than the purified and pepsin-digested ERIG products used previously. HRIG is up to 10 times more expensive than ERIG, and it is in short supply and rarely stored in Asian and African hospitals [15].

Vaccination alone will save the majority of but not all rabies-exposed patients [2, 23]. There is no known method of identifying patients who will die if they do not receive RIG. The patient who has incurred bites from a rabid animal into nerve-rich regions, such as the head or hands, or who has deep or multiple wounds, regardless of site, is at the greatest risk and has the most urgent need for RIG [2, 10, 23]. It must be emphasized that careful wound cleaning with water and an antiviral substance is the important first step to removing or destroying virus that has been inoculated. This is critical for patients with AIDS and low CD4 cell counts who may not be able to produce adequate rabies virus–neutralizing antibodies [28].

Travel medicine advisors should be aware that some PEP treatment schedules now used in Asia and Africa are different from the schedules for conventional intramuscular regimens approved in North America and Europe [14, 22, 29]. One of the multisite intradermal regimens, known as the 8-site schedule, delivers vaccine to 8 lymphatic drainage sites. It has been advocated for use in cases of severe or multiple transdermal wounds when no RIG is available [29]. However, production of higher levels or earlier production of rabies-neutralizing an-
tibodies, even if attainable, may not lead to better protection [25]. One must not assume that the 8-site intradermal schedule is a replacement for RIG. A recent rabies-related death involving a 7-year-old Thai girl, who had received the 8-site schedule but no RIG after incurring multiple facial bites, emphasizes the importance of administering RIG in such cases. She died of encephalitic rabies (determined on the basis of clinical evidence) 15 days after having been bitten [30]. However, it is not known whether optimal treatment (including RIG injected into wounds) would have saved her life.

Administration of PEP after exposure is essential, and travelers should seek medical attention immediately. If the traveler later returns home to complete the PEP regimen (or will not be staying at one location long enough to finish the original series), a treatment record with names and contact numbers should be obtained. In the event that the same vaccine is not available at the next destination, a different WHO-recommended vaccine can be used. If there is a change in the route or schedule of administration, this should be the exception. In cases in which such a change has occurred or cannot be avoided, antibody levels should be monitored, if possible [31].

It is impossible to predict who will be completely free of risk in their travels and who should receive expensive preexposure vaccination before leaving. At least 2 studies have been published on the cost-effectiveness of preexposure vaccination [32, 33]. Although cost is a factor, important noneconomic issues are also a necessary part of the process for deciding whether to administer a preexposure series. Preexposure vaccination has long been used for selected populations, such as scientists working with rabies virus, veterinarians, zoologists, cave explorers, international aid workers, missionaries, diplomats, soldiers, and Peace Corps volunteers, as well as others who may come in contact with the virus or with rabid animals as part of their vocation or travel itineraries. We know of only 1 rabies-related death in a person who had received preexposure vaccination with a tissue-culture vaccine. She received 3 injections of HDCV intradermally while taking chloroquine malaria prophylaxis, but she did not receive the recommended booster vaccine after having been bitten by her dog in Africa [34]. Because chloroquine may cause interference with the immune response [22], the WHO recommends that preexposure treatment should be administered intramuscularly when a patient is receiving malaria prophylaxis concurrently [22]. The decision about whether to recommend preexposure vaccination must be based on a review of the traveler’s itinerary and planned activities. Tourists staying in hotels and traveling in tour buses are less likely to experience a dog bite. Those who intend to backpack, run on urban or rural roads, or visit temples harboring unvaccinated dogs are at increased risk. Children are more likely than adults to be bitten by animals, and the bites they receive tend to be more severe [2, 8, 23]. Preexposure vaccination with any of the WHO-recommended tissue-culture products (HDCV, PVRV, or PCECV) is given as 1 full dose intramuscularly or 0.1 mL intradermally on days 0, 7, and 21 or 28 [22]. The intradermal route is not being used in the United States, because single-dose 0.1-mL ampules are no longer available. Current WHO-recommended tissue-culture rabies vaccines are among the most immunogenic biological agents known. Intradermal and intramuscular vaccine will produce memory cells that usually last for decades in healthy hosts. They are capable of inducing a rapid anamnestic response after administration of boosters [35–40].

Rabies-exposed individuals who have previously been vaccinated with a tissue-culture rabies vaccine should receive 2 intramuscular or intradermal vaccine injections given on days 0 and 3 [14, 22, 29]. RIG is not required for patients who have been previously vaccinated and are later exposed to rabies [22]. Subjects who have received preexposure vaccination need only to receive boosters and do not require RIG, which is in limited supply worldwide. This is a powerful argument for preexposure vaccination for travelers at risk of an exposure.

Encountering a case of rabies in a human in a country believed to be “rabies free” is a rare but not unheard of occurrence, as evidenced by the recent rabies-related death in Scotland [41]. Early diagnosis is imperative. Although physicians experienced with rabies in humans are generally able to diagnose encephalitic (furious) rabies, paralytic rabies (approximately one-third of all cases) can be difficult to identify [2, 10]. It resembles Guillain-Barré syndrome (GBS), and patients with GBS and patients with rabies who are in coma require sophisticated tests for accurate diagnosis [2, 10, 11]. The best specimens to test include CSF, urine, saliva, corneal imprints, and neck skin biopsy specimens, which must include hair follicles [2]. Saliva, urine, and CSF samples and tear secretions can be tested by RT-PCR or nucleic acid sequence–based amplification (NASBA). Serum and CSF specimens can be tested for the presence of IgM and IgG antibodies (in previously unvaccinated individuals), but the test results are often not positive when the patient first presents [2, 42]. Performance of RT-PCR or NASBA on several sequential samples of saliva, urine, and CSF will result in the best diagnostic yield for patients suspected of having rabies. Secretion of virus is intermittent even in CNS and saliva [10, 20, 21]. Rapid clinical and, where available, laboratory diagnosis is important to prevent potential exposure to the health care team and to reduce the anxiety and costs associated with avoidable PEP treatment. Comfort care should be the management goal for patients with rabies [43]. Invasive procedures and even respiratory support should be avoided in virtually every case. Liberal use of barbiturates and intravenous morphine are best for relief of terrifying attacks of anxiety, agitation, and respiratory spasms.

Despite our understanding of the epidemiology and prevention of rabies, we are still confronted with this horrific disease.
Travelers must be made aware that even regions considered to be “rabies free” are vulnerable if rabies is introduced. One example occurred in 1997 in Flores, Indonesia. This small, historically rabies-free island near Timor has a population of 1.4 million. Rabies was introduced when fishermen imported 3 dogs (at least 1 of which was incubating rabies) from rabies-endemic Sulawesi [44, 45]. Within 2 years, at least 101 people died of rabies. As a first response to control the spread of rabies, ~500,000 of the estimated 800,000 local dogs were killed. This massive canine culling failed to eliminate rabies on Flores, and human deaths were still reported in 2001. Sadly, canine rabies is still present on the island today. An islandwide dog-vaccination campaign may have prevented the spread of the disease when it was first discovered almost 6 years ago. Without vigilant surveillance and some contingency planning, the tragic events in Flores could repeat themselves in other rabies-free regions, such as neighboring Bali.

The limited supply of RIG is a critical problem that needs to be addressed on a global scale. Established international ERIG manufacturers must be encouraged to continue production and worldwide distribution of affordable ERIG. Countries where rabies is endemic that have technical expertise should consider production of their own RIG. With government motivation, technology transfer, and funding, well-equipped blood banks could make HRIG. Snake antivenin plants could use established technology to produce purified ERIG. One example is the Thai Red Cross, which has been manufacturing HRIG from serum obtained from unpaid donors for >1 decade and is currently upgrading its snake antivenin plant to make purified ERIG. New ERIG manufacturing facilities have appeared in China and have started to export their products. India is producing their own tissue-culture rabies vaccines (PCECV) and exporting to several Asian countries, including Thailand. Technology for production of monoclonal rabies antibodies (MAbs) is known, and reports indicate that a cocktail of MAbs is more effective in neutralizing virus than is HRIG or ERIG. Selected MAbs could someday replace RIG altogether [46, 47]. Travelers and expatriates will, however, continue to be at risk of exposure to rabies in countries where canine rabies is endemic, until effective dog population–control and vaccination measures are inaugurated. For these programs to be successful, we will need to learn more about dog ecology and to promote responsible dog ownership. Travel medical advisors must evaluate the travel plans of clients visiting countries where canine rabies is endemic and explain various options for protection against this disease. Before leaving home, every traveler should be informed that exposures to potentially rabid animals can have deadly consequences if not treated promptly and appropriately. They should carry contact information for reliable institutions that can be consulted in the event of a medical emergency abroad. Additional help can be found on several Web sites, including http://www.cdc.gov/travel, http://www.fitfortravel.scot.nhs.uk/, http://www.who.int/ith, http://www.who.int/emc/diseases/zoo/rabies.html, and http://www.who.int/disease-outbreak-news/n1997/may/n6may1997a.html.

Is there any good news about rabies? Yes. Expatriates and travelers moving to rabies-free countries with their dogs and cats may no longer have to quarantine their pets for many months. Many rabies-free countries now allow dogs and cats to be imported if they have positive identification by an implanted “microchip,” a valid rabies-vaccination certificate, and documentation of an acceptable antibody level from an accredited laboratory [48]. Such travelers should contact the respective consular missions for instructions before departure. In addition, the WHO is currently intensifying efforts to make governments aware of the need to institute active and effective rabies-control measures, and it has appointed an international task force to focus on rabies prevention in Asia.

Dedication

This essay is dedicated to the memory of Dr. Arthur King, a friend who devoted his life to the study of rabies. He passed away in June 2002. His counsel and humor will be greatly missed by his colleagues worldwide.

References