Rabies

Relevance, Prevention, and Management in Travel Medicine

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KEYWORDS

• Rabies • Travel • Epidemiology • Exposure • Vaccination

KEY POINTS

- Terrestrial or bat rabies is present in almost all countries of the world.
- Travelers are at risk in enzoonotic regions of being bitten; the rabies infection risk for the individual traveler and the indication for preexposure prophylaxis has to be assessed on an individual basis.
- Preexposure prophylaxis consists of one intramuscular or one intradermal injection on days 0, 7 and 21 (or 28) each.
- Postexposure prophylaxis has to be applied as quickly as possible (within 24-48 hours) after contact with a potentially rabid animal.
- In many regions of the world, antirabies immunoglobulin is not readily available. 2/3 of all travelers do not receive correct postexposure treatment.

CAUSE

Rabies is a zoonotic viral disease, transmitted only in mammals, mostly in the Orders *Carnivora* and *Chiroptera*. Terrestrial rabies (genotype 1), predominantly transmitted by dogs, is the most important rabies cycle threatening humans. The causative neurotropic virus is a negative-stranded RNA virus of the family *Rhabdoviridae*, genus

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Lyssavirus.[1–4] This genus contains several rabies-related viruses (**Table 1**).[5–8] All variants are known or suspected to cause rabies-like diseases.

Transmission occurs by the virus entering through the skin or the mucosa after bites, scratches, or preexisting injuries contaminated by the saliva of an infected mammal.

Only 51 human rabies cases that have not been transmitted by animal bites have been described. Eighteen were caused by improperly inactivated vaccine in Brazil, 15 by transplants (8 cornea, 3 kidney, 1 each for kidney-pancreas, liver, iliac artery, lung).[10–12] Eight seem to have occurred by contamination of impaired skin, 2 by aerosols in laboratory staff, and 2 have potentially originated from a stay in bat-infested caves.[13] Six cases were human-to-human transmissions and included 3 human bites. Ingesting raw meat has not been shown to be responsible for human cases.

EPIDEMIOLOGY

Rabies (terrestrial and bat transmitted) is present in more than 150 countries on all continents (**Fig. 1**). More than 95% of all human deaths are observed in Asia and Africa, mostly in rural areas. An estimated 55,000 to 70,000 persons[14,15] die from rabies every year. Severe underreporting is assumed, and 40% of all cases are children less than 15 years of age.[16,17] Forty-two deaths of imported rabies cases were reported in Europe, the United States, and Japan between 1990 and 2010.[18] Terrestrial rabies is not present in Oceania, Japan, and some Central and Western European countries. No cases have been verified in Antarctica or in New Zealand. The rabies-free status can suddenly change by (re)introduction of the disease, as documented among animals in Northeastern Italy in 2008. All but 1 country report animal rabies to the World Organization for Animal Health (Office Of Epizootics [OIE]) but only a few report to Rabnet.[19]

An area free of rabies is defined[20] as an area that (1) has no case of autochthonous infection by any Lyssavirus confirmed either in humans or in any animal species,

Table 1
Rabies and rabies-related viruses

Genotype	Virus	Phylogroup	Identified In	Main Host
1	Rabies virus	I	Worldwide	Canine, bat
2	Lagos	II	Africa, Middle East	Bat
3	Mokola	II	West Africa (Nigeria)	Bat
4	Duvenhage	I	Africa	Bat
5	EBLV-1	I	Europe	Bat
6	EBLV-2	I	Europe	Bat
7	Australian bat	I	Australia	Bat
8	Aravan	I	Kyrgyzstan	Bat
9	Khujand	I	Tajikistan	Bat
10	Irkut	I	Asia	Bat
11	West Caucasian bat virus	?	Eastern Europe	Bat
	Shimoni bat virus[a]	II	Kenya	Bat
	Bokeloh bat virus[a]	I	Germany	Bat
	Ikoma virus	?	Tanzania	African civet cat[9]

Abbreviation: EBLV, European lyssa bat virus.
[a] Not definitively classified.

Fig. 1. Rabies and rabies-related diseases. (*Courtesy of* M. Funk, and Astral/SA, Tropimed; with permission.)

including bats, at any time during 2 consecutive years; (2) provides an adequate surveillance system; and (3) has an effectively controlled import policy.

More than 99% of human deaths are caused by dog bites.[21] In South America, the saliva of bats is the most important source of infection.[22] Rodents are known to be poor transmitters, and monkeys do not play an important role in transmission to humans: no confirmed transmissions to humans have been described.

Fifteen million people per year receive some form of postexposure prophylaxis (PEP), most of them in India and China. An estimated 327,000 rabies deaths annually are thus averted.[14]

Europe

The introduction of the wildlife vaccination program[19] with vaccine baits has led to the elimination of canine/fox rabies in some European countries.[23] Only bat rabies is present there,[24,25] and spillovers are rare (there are no vampire bats in Europe). Countries free of terrestrial rabies are Great Britain, Switzerland, Spain (excluding Melilla and Ceuta on the African continent), Portugal, France, Germany, Belgium, the Netherlands, Sweden, Finland, Norway (continental), Denmark, Austria, and, until 2008, Italy.[26,27] Since 2008, Italy[28] has reported new rabies cases among foxes in the northeast (Friuli-Venezia, Giulia, Veneto), entering from the northeastern neighbouring country Slovenia. From 2008 to February 2011, 287 mostly fox rabies cases were found, most in the Veneto (216), but also in Friuli (58), Trento (8), and Bolzano 85).[29–31] Fox vaccination programs were intensified[32] and cases are declining.

Eastern Europe is still reporting human cases of terrestrial rabies.[33,34] Most wildlife cases in 2005 occurred in the Russian Federation, Ukraine, Lithuania, Belarus, Croatia, and Estonia. However, human rabies in Eastern Europe is not a major public

health problem, because public education is maintained and PEP is available within a short time.

Americas

Dog rabies cases have been reduced by 90% in the last 10 years. All rabies strains, even bat strains, are of genotype 1.[35]

In the United States, 6154 animal cases (most in wildlife: raccoons 36.5%, skunks 23.5%, bats 23.3%) and 2 human rabies cases, both bat associated, were reported to the Centers for Disease Control and Prevention (CDC) in 2010.[36] Canada had 123 confirmed wildlife rabies cases in 2010, mostly in skunks (60) and bats (48); the last human case dates from 2007 and originated from a bat bite.[37] Rabies is not a serious problem there and PEP is readily available.

Latin America started its rabies control program with dog vaccination in the 1980s. Almost 42 Mio dogs are vaccinated annually, leading to a marked decrease of cases. In 2003, only 27 human deaths of rabies were reported[35]: Bolivia reported 2 cases, Brazil 14, El Salvador 5, Haiti 3, Mexico 1, and Venezuela 2. The highest concentration of cases is found in slum areas around big cities like Fortaleza and Ceará in Brazil, Port-au-Prince in Haiti, and in San Salvador. Recently, an accumulation of dog cases and 1 human case have been documented around cities in Bolivia (Chuquisaca, Cochabamba, and Santa Cruz). Bat rabies remains an uncontrolled risk for indigenous people sleeping in open dwellings in the Amazon regions mainly of Peru and Brazil.[22]

A big part of the South (Chile, Uruguay, most of Argentina, Southern Brazil) is free of dog rabies, as are Panama and Costa Rica. Rabies is not a serious problem, but PEP is not available in remote areas.

Asia

More than half of all reported human rabies cases originate in the Far East and in South Asia (>30,000). Data are limited,[38,39] with substantial underreporting. Death rates in humans may be substantially higher than officially reported.[14]

Since 1995, human rabies cases in Thailand have steadily declined, also because of extensive vaccination of dogs. In 2006, most human deaths were reported in India (20,000), China (3209), Pakistan, Bangladesh, and Myanmar.[40] Malaysia is only marginally affected at the northern border areas of the mainland.

Availability of immunologicals (including rabies immunoglobulin [RIG]) against rabies is unreliable in tourist areas and big cities, and poor in rural areas.

Africa

The dimension of the rabies problem in Africa is unknown in many areas. Considerable underreporting is likely.[14] It is assumed that more than 20,000 people die of the disease every year. Most cases are acquired in rural areas. RIG is not readily available and access to active vaccines is limited.

Australia

Only Australian bat virus has been reported. Immunologicals are readily available.

RESERVOIR

All mammals are susceptible to rabies virus infection but only a few are important reservoirs. The wild reservoir is primarily maintained in *Carnivora* (dog, fox, wolf, coyote, jackal, mongoose) but also in *Omnivora* like raccoons, skunks and in *Chiroptera* (bats).

In North America, the main reservoirs are raccoons, skunks, and bats; in Latin America it is bats. In Western Europe the main wildlife reservoir is the red fox, in Eastern Europe the red fox (50%), and, increasingly, the raccoon dog (18%),[34] especially in Belarus and the Baltic states.

PATHOLOGY

The virus is transmitted by saliva of rabid animals through the skin and mucosa or into the muscle of the victim. The average incubation period is between 1 and 3 months. It ranges from a few days if the head or highly innervated body parts are affected (hands, arms), to more than 1 year.[41,42] The pathogenesis is not fully understood.[43] In the beginning, the virus does not enter the cells and may be removed by washing the wound with alkaline soap. Local replication in muscle cells is possible and was documented in animals.[44] The virus then enters the axon of peripheral nerves and moves toward the central nervous system (CNS) at a speed of 1 to 40 cm per day, leading to an acute and almost always fatal encephalomyelitis. The rabies virus attaches specifically and unspecifically to neuronal cell membranes. Specific receptor bindings may contribute to the pathogenicity only in mammals, but not in birds.[45,46] Once inside the neuronal cells, it replicates, moves transsynaptically, and eventually along somatic and autonomic nerves back to the skin, various organs, tissues, the salivary glands, and also to nerve tissue around hair follicles. Final massive replication in the salivary glands leads to the high infectiousness of saliva. Deadly functional damage is done to the hypothalamus and brain stem, thus influencing cardiac and respiratory control. No antibodies appear during the incubation period.[47]

CLINICAL SIGNS AND SYMPTOMS

Clinical signs and symptoms show a broad variety, even in patients infected with a Lyssavirus of the same genotype.[48,49] This adds to the frequent misdiagnosis of the disease and confusion with other CNS diseases and infections.

Human rabies infections other than by genotype 1 are rare. Therefore, only symptoms of this type are described here. Once symptoms of the disease develop, human rabies is nearly always fatal within 2 to 12 days.

Two forms of the genotype 1 disease are known: furious rabies and paralytic rabies. The latter form is present in 30% of human cases as well as in dog rabies, and it is often misdiagnosed.

Furious rabies starts with unspecific symptoms such as headache, malaise, fever, disconcertment, local sensations (tingling, burning, itching, anesthesia) at the bite or entry site, followed by excitability, confusion, hypersalivation, priapism, aerophobia, and eventually hydrophobia and convulsions.

Paralytic cases seem less severe and present with loss of sensation, weakness, and pain. The muscles are progressively paralyzed, starting at the virus entry site. A slow development of coma precedes death.

DIAGNOSIS

Before onset of clinical disease, there is no test to confirm rabies infection. Presumptive diagnosis from the patient's history of a potential rabies contact in any unclear acute neurologic illness is vital, even months or years after a potential exposure. Classic signs with hypersalivation and aerophobia or hydrophobia are not always present. Symptoms develop within 2 to 10 days to the full illness and death. Laboratory diagnosis in the first week of illness is rarely achieved.

Laboratory Diagnosis

Serology is not applicable for testing individuals for rabies at an early stage of infection. Seroconversion occurs late in clinical disease. A single test result is not sufficient, and should be repeated within 3 to 7 days. Tests of skin and saliva samples may be positive at day 4 to 5 of the disease. Antibodies are present in the serum on days 5 to 8, and later in the cerebrospinal fluid (CSF). New, more sensitive molecular methods are in development.[50]

For ante mortem diagnosis, all samples have to be considered infectious and should be securely sealed before transportation. A deep neck skin biopsy containing a minimum of 10 hair follicles should be at least 5 mm in diameter and taken from the neck hairline, deep enough to contain the skin nerves of the hair follicle. Lyssavirus antigen is found by direct fluorescent antibody (DFA) test or reverse-transcriptase polymerase chain reaction (RT-PCR). The DFA is the gold standard test.[49,51–53] In saliva, the detection of rabies RNA (RT-PCR) or the virus in cell culture is considered diagnostic. In serum and CSF, detection of antibodies to rabies virus in unvaccinated persons leads to the diagnosis. The tests include the indirect fluorescent antibody test (IFA), complete rabies neutralization at 1:5 dilution, or an increase in antibody levels.[49,51–53] Brain biopsy is not indicated because of lack of treatment consequences. Post mortem diagnosis is made from tissue of the brain stem,[54] cerebellum, or hippocampus and includes antigen detection by DFA . Other diagnostic tests are the direct rapid immunohistochemical test, RT-PCR,[55] enzyme-linked immunosorbent assay, Sellers stain technique (Negri bodies),[56] rabies tissue culture infection test,[57] and mouse inoculation test.[58]

MANAGEMENT

Immediate treatment is crucial in case of a possible exposition to rabies: a substantial part of the virus load can be washed out and mortality reduced by 50%.[59,60] Immediate, thorough (approximately 15 minutes) washing and flushing of all bite wounds, scratches, or injuries with alkaline soap and large amounts of water is required. Subsequent disinfection with the usual disinfectants may further reduce the risk of disease development. Apart from mandatory postexposure vaccination, antibiotic coverage according to the potential bacteriologic spectrum may be appropriate (**Table 2**).

Table 2
Categories of exposure (World Health Organization)

Cat	Category of Exposure to Animals Suspicious for Rabies	Type of PEP
I	Touching or feeding animal licks on intact skin	None
II	Nibbling of uncovered skin, minor scratches, abrasions without bleeding	Immediate vaccination, local wound cleansing. Additionally, in persons with an immunodeficiency, rabies immunoglobulin should be applied.
III	Single or multiple bites or scratches (penetration of the skin), licks on broken skin, contamination of mucous membrane with saliva from licks, bat exposure	Immediate vaccination, administration of rabies immunoglobulin, local treatment of the wound

Data from Rabies. Guide for post-exposure prophylaxis. World Health Organization, WHO; 2011. Available at: http://www.who.int/rabies/human/postexp/en/. Accessed June 20, 2012.

PEP

The type of PEP depends on the category of exposure to a suspicious animal. PEP must be applied whenever rabies exposure is suspected, and in any category II and III contact with a potentially rabid mammal. It includes application of RIG and vaccination in subjects without previous vaccination. RIG is mandatory in category III contacts in persons who have not previously been vaccinated and in category II contacts in persons with a immunodeficiency who have not previously been vaccinated.

Despite exceedingly rare failures,[41,61,62] correct and timely application of PEP in nonimmunized victims after contact with rabies virus is considered to prevent the development of disease. The rule of thumb (not evidence based) is that application of immunologicals should occur within 48 hours.

Previously vaccinated subjects need 2 vaccine doses on days 0 and 3, or 4 intradermal injections of 0.1 mL on day 0.[42] Less urgency for such boosting of memory cell function seems necessary.

Mortality in symptomatic patients is close to 100%. Only 6 patients with confirmed rabies disease have survived. All have been vaccinated after the event, and none of them had received immunoglobulin prior to the onset of the disease. Only 1 patient recovered fully, the other 5 survived with severe sequelae.[63]

Vaccination

Passive immunization Administration of human rabies immunoglobulin (HRIG), or equine rabies immunoglobulin (ERIG) in many developing countries, provides an immediate protection by virus-neutralizing antibodies to bridge the time to an active immune response. Use of HRIG (20 international units [IU]/kg) provides passive immunity that persists for a short time (half-life approximately 21 days).[64,65] ERIG or F(ab')2 products of ERIG are less effective and have a shorter half-life. Therefore, ERIG requires a higher dose (40 IU/kg). Various products of HRIG are available (eg, HyperRab S/D [Talecris Biotherapeutics], Imogam Rabies-HT [Sanofi Pasteur], Berirab [Bering]). The World Health Organization (WHO) does not recommend the use of immunoglobulin later than 7 days after the initiation of postexposure vaccination. As much as possible of the RIG should be injected into or around the wound site. If necessary, RIG can be diluted if several sites are present. The remaining immunoglobulin is applied intramuscularly at a distant site. For PEP in a category III exposure or in a category II exposure in a person with an immunodeficiency, except for persons previously vaccinated, RIG should always be administered concurrently with the first dose of vaccine.

Active immunization For all vaccines, the potency should be at least the WHO-recommended minimal potency of 2.5 IU per full intramuscular vaccine dose.[66] In industrialized countries, 0.5 to 1.0 mL intramuscular (IM) doses are generally used for both preexposure and PEP regimens. In developing countries, different IM and intradermal (ID) regimens are used.

The neutralizing antibody response appears 7 to 10 days after initiation of vaccination, and detectable levels persist for years. There are no trials to document a change of efficacy if different cell cultured vaccines are used.

Intramuscular regimens

- Essen regimen (original): 1 dose on days 0, 3, 7, 14, and 28
- Zagreb regimen: 2 doses on day 0, followed by 1 dose each on day 7 and 21
- Essen regimen (shortened): an alternative regimen for people who receive wound care plus WHO-prequalified rabies vaccine plus high-quality rabies immunoglobulin and are immunocompetent is a 4-dose intramuscular regimen of 1 dose on days 0, 3, 7, and 14[67]

Intradermal regimens Updated Thai Red Cross regimen: 2 intradermal doses on days 0, 3, 7, and 28, injected (eg, at the dorsal side of the forearm).

For IM and ID regimens, a fifth dose after at least 3 months may be administered to convey an immunologic memory, but studies confirming this protection are lacking. Thus a booster schedule (1 dose each on days 0 and 3) is necessary after every potential rabies contact (**Table 3**).

Adverse effects The need for rabies PEP after a potential contact outweighs the risks of the vaccination. Thus, hypersensitivity to components of the vaccine is a only relative contraindication. Precautions, contraindications, and adverse effects related to rabies vaccination are summarized on the following Web page: http://www.cdc.gov/rabies/specific_groups/doctors/vaccination_precautions.html.

Pregnancy

PEP is not contraindicated in pregnancy or during breast feeding.

Immunosuppression

Immune-compromising agents and treatments (corticosteroids, cancer therapy, irradiation, immune modulators, immunosuppressive medication), diseases (eg, HIV), or conditions (eg, solid organ and hematopoietic stem cell transplant recipients) may interfere with immune response and vaccination targets.[69–72] For PEP, the original Essen regimen with 5 IM doses on days 0, 3, 7, 14, and 28, plus RIG (in category II and category III exposures) and rapid fluorescent focus inhibition test (RFFIT) confirmation of adequate antibody response on day 21 should be strictly adhered to.[42]

TREATMENT OF RABIES DISEASE

Acute Treatment Measures

Life can be prolonged only for a short time. Analgesics and heavy sedation are necessary. The role of antivirals (Ribavirine), interferon-α, and ketamine is unclear. The only treatment option is palliation and supportive care.[73,74]

PREVENTION

There are 2 main prevention strategies: (1) avoid contact with unfamiliar and wild living animals, and (2) get a preexposure vaccination in case of professional risk and other exposures, as listed in **Table 4**.

Table 3
Rabies vaccines worldwide

Brand	Distribution	Culture Media
Imovax Rabies Vaccine	Sanofi Pasteur	Human diploid cell
Imovax Rabies Vero	Aventis Pasteur	Purified vero cells rabies vaccine
RabAvert	Chiron	Purified chicken embryo cell
Rabivac	Chiron	Human diploid cell
Rabipur	Novartis	Purified chicken embryo cells
Vaccin Rabique Mérieux	Sanofi Pasteur	Human diploid cell
TRC Verorab	Sanofi-Aventis	Purified vero cells rabies vaccine
Verorab	Sanofi Pasteur	Purified vero cells rabies vaccine
Rabies Vaccine Absorbed	Bioport GSK, United States (not available at this time)	Diploid fetal rhesus lung cells Rhesus cell rabies vaccine
Vaxirab (Lyssavax-N)[68]	Licensed in India (Berna Biotech)	Purified duck embryo cells

Table 4
Rabies risk groups

Risk Category	Risk Groups/Profession	Preexposure Regimens
Continuous	Rabies research, rabies biologics work	Primary course. Testing after 6 mo and booster dose if titer is <0.5 IU/mL (RFFIT)
Frequent or episodic	Rabies diagnostic workers, animal handlers, veterinarians and staff in enzootic areas, working with wild animals in enzootic areas, bat handling, caving	Primary course. Testing after 2 y and booster dose if titer is <0.5 IU/mL (RFFIT)
Infrequent	Veterinarians and staff in nonenzootic areas, work with wild animals in nonenzootic areas, travelers in regions with rabies and no access to immediate appropriate medical care (limited access to vaccine and HRIG)	Primary course
	Travelers with extensive outdoor exposure in rural high-risk areas where immediate access to appropriate medical care may be limited, regardless of duration of stay	No testing, no booster vaccination
Rare	Worldwide, if good access to medical care (biologics available)	None

Abbreviation: HRIG, human rabies immunoglobulin.

Data from Manning SE, Rupprecht CE, Fishbein D, et al. Human rabies prevention–United States, 2008: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2008;57(RR-3):1–28.

Although vaccinating dogs is the most cost-effective public health strategy for preventing rabies in humans, the preexposure prophylaxis (PrEP) of human individuals remains a crucial option for practical reasons. Risk groups should be vaccinated before possible exposure.[75]

PrEP

At least 3 doses are necessary. In industrialized countries, a 3-dose IM regimen with human diploid cell vaccine (HDCV) or purified chicken embryo cell vaccine (PCECV) with one ampoule on days 0, 7, and 21 (or 28) injected into the deltoid area in adults or in the antelateral area of the thigh in children less than 2 years old is recommended.

Intradermal regimens with the same intervals are used in developing countries because supply of vaccine is limited. One intradermal dose consists of 0.1 mL. The Asian Rabies Expert Bureau recommends that one intradermal dose should contain $\geq$0.50 IU, irrespective of the vaccine used.[76]

Healthy persons tested 2 to 4 weeks after complete and correct PrEP with cell cultured vaccines showed adequate antibody response (RFFIT). Testing in immune-competent persons who do not work with potentially rabid material is not necessary.[78,79] Cross-protection to groups other than phylogroup I depends on how far the genetics differ.[77,80] Protection against the Eurasian bat virus strains Aravan (ARAV), Khujand (KHUV), and Irkut (IRKV) is not reliable.[81] Protection against West Caucasian bat virus (WCBV) is questionable.

The gold standard to measure the immune response after active vaccination is the RFFIT.[82] According to the WHO, the minimal titer showing an adequate immune response is 0,5 IU/mL 14 days after the final vaccination.[83–85]

PREVENTION OF RABIES IN TRAVELERS

The risk of rabies disease among travelers is low, but the number of potential rabies exposures is considerably higher than generally anticipated.

Twenty-two cases of rabies in travelers have been reported in the last 10 years. The highest risk was observed in migrants and visiting friends and relatives (VFRs). Most victims were men. Children have not been found to be at a higher risk among travelers in studies, but vaccination should still be recommended because children may not report an exposure to their parents and may miss PEP, and because they are more often injured on the head, because of smaller body size.[86]

Two-thirds of travelers did not receive correct PEP after a suspicious contact.[87,88]

The incidence of being licked or bitten by a potentially rabid animal (mostly dogs) was estimated at 3.6% and 0.7% respectively in a study among backpackers in southeast Asia.[89] The incidence of being injured by a potentially rabid animal varies between 2 to 32 per 1000 travelers per year according to different studies.[90,91] However, routine vaccination against rabies for all travelers to every region of the world with an increased risk of rabies is neither feasible nor sensible.

The WHO recommendations state that people "with extensive outdoor exposure in rural high-risk areas, regardless of duration of stay"[42] should be vaccinated. However, a study done in Nepal showed that trekking was not associated with an increased risk for potential rabies exposure.[90] Another study described more exposures in cities than in rural areas.[92] Length of stay cannot indiscriminately be used as an indicator for the risk of being exposed to a potentially rabid animal either. Diverging results from different studies looking at the time point of exposure among foreign backpackers in Thailand showed that 54% of all contacts happened within the first 10 days after arrival,[89] whereas the exposure occurred after a median of 5 weeks among Israeli travelers.[91]

Other contradictory results exist concerning the risk for travelers to different geographic regions. Although some countries report more cases of potential rabies exposure in travelers returning from South and Southeast Asia,[93] others report more cases from North Africa.[94] These ratios depend on the absolute number of tourists to these destinations. Furthermore, different results are reported with regard to different age groups[93,95] or sex.[96,97]

The presumed risk factor of outdoor exposure in rural high-risk areas[42] does not seem to be based on much evidence and neither travel destination nor age, sex, or length of stay are universally applicable risk factors. An alternative basis for recommendations of PrEP may be the timely availability of adequate PEP at the destination. This approach depends on several factors: (1) first and foremost, travelers must be aware of the risk of rabies at the travel destination and of the modes of transmission; (2) travelers immunized with 3 preexposure doses will be more relaxed than nonvaccinated travelers by buying some time and reducing hassle before getting postexposure treatment in case of an exposure, especially in areas where RIG is not readily available; (3) travelers need to know where correct treatment is available; (4) the required biologicals do not only have to be available within a limited amount of time but their correct application must be assured; (5) planned repeated trips to endemic areas in the future (cumulative risk) may also influence the decision for PrEP.

Even if vaccine and immunoglobulin were available in certain destinations, PrEP might be indicated for ethical reasons: every traveler who requires postexposure treatment in the developing world further depletes the already meager stocks of vaccine, possibly depriving someone else of a life-saving treatment.

The difficulty of estimating the risk for the international traveler is probably best assessed and discussed at individual level, based on travel style (eg, backpacker,

VFR), length of stay, age, and destination. Most of all, every traveler must be made aware of the risk and know what to do in case of an exposure.

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