

Rabies Exposures in International Travelers: A Review

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ABSTRACT

Up to 2% of international travelers report an animal contact which raises the possibility of rabies exposure. Travel-associated rabies is rare; however, infection is essentially fatal once expressed yet death is preventable by timely postexposure prophylaxis (PEP) -- thorough wound cleansing, local injection of rabies immune globulin (RIG) and a vaccine series. To begin to provide initial guidance if contacted by a patient potentially exposed to rabies while abroad, key questions the clinician should ask in a stepwise fashion are: (1) What animal was involved? (2) What was the actual exposure and in what country did it occur? (3) How many wounds, location (including mucosal surfaces), severity and what wound care performed? (4) Is the traveler immunocompromised? (5) Was either pre-exposure rabies prophylaxis or PEP previously given? (6) Is rabies PEP clearly indicated and/or is expert advice and guidance needed? (7) Where is the traveler, what level of acceptable care is accessible and how long to access it? And (8) What formulation of rabies immune globulin and vaccine is available and what injection protocol is in-use? Framed here by experience with four travelers, answers to these and additional questions set the stage for the clinician's initial guidance and action. The goal and clinical relevance of this review is straightforward – to maximize the opportunity for travelers who warrant rabies PEP to promptly receive it.

Keywords

International Travel, Postexposure Prophylaxis, Rabies.

Abbreviations

CDC: Centers for Disease Control; ERIG: equine rabies immune globulin; HDCV: human diploid cell vaccine; HRIG: human rabies immune globulin; ID: intradermal; IM: intramuscular; NHP: nonhuman primate; NYC: New York City; PEP: postexposure prophylaxis; PCECV: purified chick embryo cell vaccine; PrEP: pre-exposure prophylaxis; PVRCV: purified Vero cell vaccine; RIG: rabies immune globulin; WHO: World Health Organization.

Introduction

As many as 2% of international travelers report an animal contact which raises the possibility of exposure to rabies virus [1], the principal but not only *Lyssavirus* capable of causing human rabies [2,3]. Other estimates suggest 16-200 rabies risk exposures per 100,000 travelers [2] and an incidence for at-risk bites of 0.4% (range, 0.01-2.3%) per month of stay in an endemic region [4].

Travel-associated rabies itself, however, is very rare with perhaps 2-4 cases recorded per year worldwide [5-7]. In travelers from the United States, for example, 36 cases (all attributed to dog bites) were reported during the 58-year period, 1960-2018 [8].

Nonetheless, rabies is almost invariably fatal once symptoms are expressed, yet at the same time, death from rabies is considered entirely preventable by prompt, complete postexposure prophylaxis (PEP). Given these realities, clinicians in this country may encounter the urgent, sometimes unsettling experience of being contacted by a traveling patient potentially exposed to rabies abroad. These individuals, including those who received pre-exposure rabies prophylaxis (PrEP), will need guidance which initially involves being able to ask the right questions in a stepwise fashion (Table 1). Satisfactory guidance is in turn predicated on familiarity with: (a) basic essentials of rabies exposures, wound care and PEP (Tables 1-3), (b) approaching an exposure in another region, including (i) country risk (Table 4), (ii) availability of cell-derived vaccines and rabies immune globulins (RIG) (Tables 4,5),

Table 1: Clinician's Checklist: Questions for and About the Traveler.

A. Initial Questions

1. **The Animal.** What animal was involved? See Table 2 for animals of concern.

- a. Was it unhealthy-appearing or behaving abnormally?
- b. Can it be captured, euthanized and promptly tested, or if a domestic animal, reliably confined for observation for 10 (dog, cat, ferret) or 15 days (livestock)?

2. **The Exposure.** Was the exposure a bite or a nonbite and was it unprovoked?

- a. Touching, petting or feeding an animal, licks on intact skin, and contact with animal tears, urine, blood or fecal material are not rabies at-risk exposures [9].
- b. At-risk exposures to potentially infected saliva are: (i) nibbles at intact but uncovered skin, (ii) licks at abrasions, sites of broken or bleeding skin or at mucosal surfaces, (iii) scratches and especially transdermal bites, and (iv) any direct skin or mucosal contact with a bat [9].
- c. Nonbite exposures from terrestrial animals rarely transmit rabies.

3. **The Country.** Where did the exposure occur?

- a. In that country, what is the status of rabies in the identified animal? See Table 4 for sources of country-by-country information.

4. **The Wound (or Exposure).** How many, where located (including mucosal surfaces), how deep or severe and what wound care has been performed?

- a. Wounds that are multiple, located on the head, face, neck, hand or genitalia (highly innervated areas) or deep in the tissues increase the likelihood of rabies transmission and/or may shorten the incubation period (head & neck wounds) [9,10].
- b. Wound washing must be prompt, prolonged and thorough; an antibacterial antibiotic maybe indicated. See Table 3.
- c. If suturing is required and post-exposure prophylaxis (PEP) is warranted, rabies immune globulin (RIG) should be injected first into and around all wounds before even partial closure.
- d. Bat bites may be difficult to locate.

5. **Monkey Bite.** Was the exposure a monkey bite in South, Central or SE Asia?

- a. In addition to rabies, bites from rhesus macaque monkeys have remote potential to transmit herpes B virus, deserve more prolonged wound cleansing and possible consideration for antiviral prophylaxis [11,12].

6. **The Traveler.** Is the traveler immunocompromised?

- a. Recommendations for both tetanus and rabies PEP differ for the immunocompromised patient (see below).

7. **Tetanus immunization.** When was tetanus toxoid or Tdap last given?

- a. Within 5 years (satisfactory protection for all wounds, including contaminated) or within 10 years (satisfactory for clean, minor wounds only)?
- b. Regardless of immunization history, patients with severe immunodeficiency, including HIV infection with low CD4⁺ T cell counts, who have contaminated (even minor) wounds should also be given 1 IM injection of tetanus immune globulin [13].

8. **Prior Rabies Immunization.** At any time in the past, had the traveler received pre-exposure prophylaxis (PrEP) or PEP?

- a. In the U.S., in immunocompetent adults: (i) PrEP in 2021 will consist of 2 (previously 3) intramuscular (IM) injections of vaccine (days 0, 7) [14]; during 1986-2001, intradermal (ID) administration was also used for PrEP, and (ii) PEP consists of 1 injection of human RIG (HRIG) and 4 IM injections of vaccine (days 0, 3, 7, 14) [15]. (Immunocompromised individuals should have received one additional vaccine dose on day 21-28 in both PrEP and PEP regimens, ideally with testing 2-4 weeks later documenting an adequate antibody response.)
- b. In such previously-immunized travelers in whom PEP is now warranted: (i) RIG is not indicated, and (ii) 2 IM (days 0, 3) (2) or, if abroad, fewer ID vaccine doses are warranted to boost pre-existing immunity (Table 3). Previously-immunized immunocompromised travelers, however, should receive RIG and a full course of PEP [15], along with follow-up antibody testing.

B. Consultation

9. **Expert advice and guidance.** Is rabies PEP indicated?

- a. Answers to the preceding questions may not lead to clear-cut conclusions about rabies risk and how best to proceed; judgments need to be individualized. See Table 4 for expert consultation sources.

C. Next Questions If Rabies PEP Is Indicated

10. **Medical care.** Where is the traveler, and what level of acceptable care is accessible or how long to access it?

- a. The injury may require immediate wound care, tetanus re-immunization, and/or antimicrobial therapy.
- b. However, starting rabies PEP is considered medically urgent, not emergent. "Medically urgent" has not been defined, nor has "immediate" or "prompt" PEP.
- c. In its by-country availability assessment for rabies vaccines and RIG (<https://www.cdc.gov/rabies/resources/countries-risk.html>), CDC uses "within 48 hours" to assign one of three categories -- available, of limited availability or not readily available. During such a period, the traveler's goal is to locate and secure satisfactory care and start PEP or begin relocation.
- d. If not immediately available, a RIG preparation can be injected up to and including 7 days after the first rabies vaccine injection.
- e. See Table 4 for possible direction, if needed, to medical care.

11. **Rabies PEP.** In-country, what rabies vaccine is available, what injection protocol is used, and what formulation of RIG is available (if any)?

- a. Cell-derived vaccines are considered interchangeable with the two available in the U.S. (Imovax™, RabAvert™). See Table 5 for WHO-prequalified vaccines.
- b. Vaccine should never be injected in the gluteal region.
- c. WHO considers ID (0.1 ml)- and IM (1.0 ml)-administered vaccine similarly? effective. See Table 3 for injection protocols in-use.
- d. Travelers should refuse animal nerve tissue-derived vaccine (large volume, daily subcutaneous injections for 14-21 days) which may still be used in Africa and South America (e.g., possibly Algeria, Argentina, Bolivia, Ethiopia) [16].
- e. WHO considers HRIG and equine RIG (ERIG) equally effective.
- f. Various formulations of HRIG, ERIG and monoclonal antibody are marketed abroad (Table 5) but may be difficult to obtain or not available in some countries.
- g. If HRIG (20 IU/kg) is not available, purified ERIG (40 IU/kg) or its highly purified F(ab')₂ fragment or rabies monoclonal antibody are considered preferable to no RIG [2]. Unpurified equine anti-rabies serum should be declined.
- h. The calculated maximum dose of RIG may be diluted in normal saline to ensure that all wounds are injected.
- i. Unless essential, immunosuppressive medications should be withheld during PEP [17].
- j. Obtaining and transmitting in real-time and by photograph, if feasible, documentation of all medical care provided is important.

Table 2: Wildlife Animals and Level of Concern for Transmitting Rabies [9,18,19].

Concern	Possible Concern*	No Concern**	
Dog	Larger Rodent:	Small Rodents:	Non-Mammals:
Cat (feral)	Groundhog/woodchuck	Squirrel	Reptiles
Bat	Badger (20)	Hamster	Amphibians
Raccoon	Beaver	Guinea pig	Fish
Fox	Otter	Gerbil	Birds
Wolf	Large Mammal:	Chipmunk	
Jackal	Zebra (21)	Vole	
Skunk	Bear	Mole	
Mongoose	Deer	Rat/Mouse	
Monkey (NHP) [†]	Unvaccinated horse, donkey, cattle or livestock	Lagomorphs: Rabbit, hare	

*Animals which may survive an initial attack from a rabid animal and go on to potentially transmit infection. Unless up-to-date with vaccination, domesticated outdoors animals (e.g., dogs/puppies, cats/kittens and ferrets) or livestock can, if bitten, subsequently pose a possible risk to humans; this risk is low but not necessarily eliminated despite current, proper vaccination.

** Non-mammals do not harbor rabies. Small rodents, rabbits and hares are almost never found to have rabies, and have never been implicated in human transmission.

[†]NHP = non-human primate.

Table 3: Rabies Postexposure Prophylaxis (PEP) in Immunocompetent Individuals with At-Risk Exposures.

	Wound Cleansing*	Vaccine Administration		Rabies Immune Globulin** (RIG)
		IM Injection	ID Injection	
1. Non-Immunized				
U.S. Approved	+	d 0,3,7,14 ^{***}	No	Yes
WHO Recommended	+	d 0,3,7,14-28 or	2-sites: d 0,3,7	Category III
	+	d 0(x2),7,21 [†]		exposures only ^{††}
WHO Alternatives	+		2-sites: d 0,3,7,21-28 or	Category III only
	+		4-sites: d 0 + 2-sites: d 7 +	
			1-site: d 21-28 or	Category III only
	+		4-sites: d 0,3,7	Category III only
2. Previously Immunized				
U.S. Approved	+	d 0,3	No	Not indicated
WHO Recommended	+	d 0,3	1-site: d 0,3 or	Not indicated
	+		4-sites: d 0	Not indicated

*Thorough wound (or mucosal surface) washing with copious water and soap for 15 minutes; irrigation with a virucidal agent (e.g., povidine-iodine) should also be used, if available [9,10,22].

**RIG (or possibly, rabies monoclonal antibody) injected promptly or up to and including day 7 after first vaccine dose.

In the U.S.: (a) rabies at-risk exposures warranting PEP are considered to also always warrant human RIG (HRIG) (20 IU/kg), (b) purified equine RIG (ERIG) (40 IU/kg) or its highly purified F(ab')₂ fragment or monoclonal antibody are considered preferable to no RIG, and (c) RIG is infiltrated in and around all wounds using as much of the weight-calculated dose as anatomically feasible; any remaining volume is injected IM distant from the vaccine site [2,22].

WHO: (a) limits recommendations for using HRIG or ERIG (or monoclonal antibody) to Category III ("severe") exposures only (see footnote ^{††}) except in immunocompromised individuals with Category II exposures, (b) advises additional RIG-sparing with no IM injection of residual RIG volume after anatomically-feasible wound infiltration of the maximal calculated dose, (c) recommends diluting the maximal dose of RIG as needed to enable injection of all wounds, and (d) suggests considering rinsing mucosal exposures with diluted RIG [9].

^{***}Immunocompromised individuals should receive a 5th vaccine dose on day 21-28 followed by serologic testing for antibody response 2-4 weeks later [9,17].

[†]4-dose protocol with 2 IM injections on day 0 plus 1 IM injection on days 7 and 21.

^{††}WHO categories of at-risk exposure [9]: Category I: no risk. Category II (exposure): nibbling at uncovered skin, minor scratches or abrasions without bleeding. Category III (severe): transdermal bites or scratches, contamination of mucous membranes or broken skin with saliva from animal licks, or any direct contact with bats.

Table 4: Sources of Information and Guidance for U.S. Clinicians and Travelers for Potential Rabies Exposures Abroad.

In the Country of Exposure:	
1. What is the current status of rabies in dogs, other terrestrial wildlife and bats?	<ul style="list-style-type: none"> CDC (https://www.cdc.gov/rabies/resources/countries-risk.html). Select Country. Information (for 240 countries and territories) indicates destinations which are currently (a) canine rabies virus-free (n = 51), (b) free of rabies virus in all terrestrial animals including dogs (n = 43), or (c) entirely <i>Lyssavirus</i> (bat)- and rabies virus-free (Antarctica, New Zealand and 24 other Pacific or Indian Ocean islands). United Kingdom (https://www.gov.uk/government/publications/rabies-risks-by-country/rabies-risks-in-terrestrial-animals-by-country). Select Country.
2. What is the availability of high-quality rabies vaccine and immunoglobulin?	CDC (https://www.cdc.gov/rabies/resources/countries-risk.html). Select Country.
3. Where may needed medical care be available (wound care, rabies PEP)?	<ul style="list-style-type: none"> Contact U.S. embassies, consulates and diplomatic missions (https://www.usembassy.gov/). Select Country and see contact information. International Society of Travel Medicine (ISTM) Online Clinic Directory (https://www.istm.org/AF_CstmClinicDirectory.asp). Select Rabies Immune Globulin, Post-Exposure Rabies Vaccinations and Country.*
Expert Advice and Guidance	
1. Does the exposure represent a risk for rabies and is there a need for prompt PEP?	<ul style="list-style-type: none"> U.S. State and Local Rabies Consultation Contacts (https://www.cdc.gov/rabies/resources/contacts.html). CDC <ul style="list-style-type: none"> (i) CDC-INFO National Contact Center (800-232-4636, 8 AM-8 PM, Monday-Friday). (ii) CDC Rabies Branch Duty Officer (404-639-1050, 8 AM-5 PM, Monday-Friday) (iii) CDC Emergency Operations Center (not intended for use by the general public, 770-488-7100, 24 hours per day/7 days per week).

* Lists ISTM members and travel clinics, but only in 21 countries outside of the U.S., Canada, Western Europe, United Kingdom, Australia/New Zealand, Israel and Japan.

Table 5: Rabies Vaccines, Immune Globulins and Monoclonal Antibodies (Trade Names).

	Approved In U.S.	Available Abroad	
		WHO Pre-qualified	Other (partial list)
Cell-Derived Vaccines*			
HDCV	Imovax	None	Imovax-Rabies, MIRV*, Rabivac, Rasilvax
PCECV	RabAvert	Rabipur (ChiroRab) VaxiRab N	
PVRCV		Verorab Rabivax-S	Abhayrab, Berab, Imovax-Rabies Vero, Indirab, Rabies Vero, TRC VeroRab, PVRCV Speeda, Vaccin Rabique Pasteur
PDECV			Lyssavac-N
Immune Globulins			
Human	HyperRab S/D	None	Abhayrig, Bayrab-P, Carig, Hyperrab, Human Rabies Immunoglobulin, Imogam, Imogam Rabies, Imorab, Kamrab, PARS, Pasteur Antirabies Serum, Rabglob, Rabigam, Rabix-IG, Rabuman Berna, Suya-HRIG, Yi Sheng Bao Er
	HyperRab		
	Imogam Rabies-HT		
	KEDRAB		
Equine	None	None	ERIG, Equirab, Favirab, Rabies Antiserum, VINRAB
Monoclonal Antibodies	None	None	Rabishield, Twinrab

*Abbreviations: HDCV (human diploid cell vaccine), PCECV (purified chick embryo cell vaccine), PVRCV (purified Vero cell vaccine), PDECV (purified duck embryo cell vaccine), MIRV (Merieux Inactivated Rabies Vaccine).

and (iii) local injection protocols (Table 3), (c) rabies-relevant information and medical documentation the traveler should collect, and importantly, (d) knowing where to turn or refer for expert and individualized advice (Table 4). Understandably, such advice may well be needed since, just as in the U.S., decisions regarding PEP can be complex [23] and managing a potential rabies exposure abroad may not be clear-cut.

The clinician may first be contacted from abroad after local care and PEP have begun or even been completed. Thus, it may also fall to the U.S. clinician to provide judgment (or obtain advice) about the type and adequacy of administered wound care and locally-initiated PEP. Conclusions about the latter, including the failure to receive RIG or deviations from vaccination protocols, may necessitate a revised itinerary and/or even repatriation for PEP completion and serologic testing to verify the antibody response to

administered vaccine. Finally, one may also encounter a returned traveler who has yet to seek any advice or care despite a bona fide at-risk exposure experienced even months before in a rabies-endemic region. Such individuals may warrant full PEP even up to a year or rarely more after exposure (see Supplemental Content 1A).

This narrative review highlights and updates decision-making which U.S. clinicians may be called upon to consider in traveling patients with potential rabies exposures. Cases of 4 international travelers who received initial care abroad before contacting or being seen at the Cornell Travel Clinic in New York City (NYC) are analyzed and used to frame discussion of selected key issues. Supplemental Content 1 provides additional relevant information.

Case Reports

Patient 1

In 2009, a healthy 38-year-old woman called our clinic from Rome, Italy to complete rabies PEP. Seven days before, while jogging in rural northeastern Italy, she was attacked and bitten on the calf by a red fox. She bandaged her bleeding wound, traveled back to Rome 1 day later and was promptly referred to a clinic. There, the open wound was thoroughly cleansed (suturing not required) and iodine disinfectant applied. Human RIG (HRIG) was injected at 20 IU/kg into and around the wound; the left-over HRIG volume was injected into the left deltoid muscle. She was given an intramuscular (IM) injection of a cell-derived rabies vaccine in the right deltoid and an antibacterial antibiotic. Her last tetanus toxoid booster was 4 years before. She received a second IM rabies vaccine injection 3 days later, and called our clinic from Rome to secure follow-up PEP. She was asked to bring her medical documents. When seen (day 7 after the initial vaccine injection), her wound appeared uninfected, and she produced her treatment records and vials of the purified chick embryo cell vaccine (PCECV) (Rabipur™) she had received. In our clinic, she was given IM doses of RabAvert™ (Table 5; in the U.S., Rabipur™ is marketed as RabAvert™) on days 7, 14 and 28, and made an uneventful recovery.

Case analysis

This patient: (a) recognized the need for prompt attention for her bite, (b) was fortunately in Western Europe with ready access to recommended care (wound cleansing, HRIG, high-quality vaccine), (c) returned with her treatment documentation, and (d) completed PEP without delay. Had she been seen after 2009, she would have received 4 (day 0, 3, 7, 14) rather than 5 vaccine doses per CDC's revised 2010 PEP guidelines for immunocompetent individuals [15].

Patient 2

In 2012, a physician-colleague called to make an urgent clinic appointment for that day for a rabies vaccine injection for her healthy 72-year-old mother, a resident of India. Her mother had just arrived for vacation and informed her that 14 days before, at her brother's home north of New Delhi, she was bitten (unprovoked) on the arm by his pet dog. Prior to her departure for NYC, her documents indicated 3 IM injections of rabies vaccine

(Verorab™, a purified Vero cell vaccine (PVRCV)) (Table 5), at a local clinic on the day of the bite (day 0) and 3 and 7 days later. On day 0, her bleeding wound was only briefly cleansed and not injected (e.g., no RIG). She was given a tetanus toxoid booster and oral antibiotic therapy. In our clinic (day 14), the closed wound appeared uninfected, and specific information was requested about the dog. Via a telephone call to India made by the daughter at our behest at this clinic visit, we learned that the dog had once received rabies vaccination and had now been observed at home for 14 days; the dog was healthy, active, and behaving normally. The patient's daughter provided the clinic with a signed summary of this information, and we agreed with her that the originally anticipated day 14 vaccine injection was no longer warranted and the failure to give RIG was of no consequence.

Case analysis

Patient 2 had a bona fide rabies at-risk exposure (WHO Category III, see Table 3 legend (9)) in a rabies-endemic country. However, after medical consultation, proper wound care and tetanus re-immunization, initially withholding PEP entirely would have been appropriate. The dog was a healthy domestic pet, behaving normally, and most importantly, could be confined for ≥ 10 days with close, reliable observation by its owner for any change or illness/death. Either event would mandate immediate PEP including RIG and testing the dog, if feasible. Nonetheless, since Patient 2's exposure was judged at-risk for rabies, the local clinic's treatment was suboptimal (brief wound washing) and incomplete (vaccine but no RIG) (Table 3). How the unprovoked nature of a bite and a dog's prior immunization may factor into decisions about PEP and the usefulness of the 10-day quarantine period in initially withholding PEP are considered in Supplemental Content 1B and 1C.

Patient 3

In 2015, a healthy 58-year-old man was seen in clinic in advance of a two-week, conventional tourist trip to Bhutan, Thailand and China. He had received Tdap vaccine 4 years before. Rabies PrEP was discussed but declined in part because of the ability to immediately return home if necessary. As per clinic routine, he was advised to (a) avoid all animals (including monkeys), (b) thoroughly wash any animal-related exposure site, and (c) promptly seek care for any injury and advice about rabies risk and possible PEP. PEP was described, and he was shown the easily-understood *Rabies* chapter in CDC's *Yellow Book* [2] and given its web address if needed.

Predictably, the morning after his arrival in Thimphu, capital of Bhutan, he was bitten on the thigh (Supplemental Content 2, Figure 1) in an unprovoked attack by a stray dog which disappeared. His hotel directed him to the national referral hospital where the bleeding 3x2 cm laceration was thoroughly cleansed (suturing not required). He was given an unidentified rabies vaccine in two small-volume injections into the skin over each deltoid, and instructed to return 3, 7 and 28 days later for similar two-site intradermal (ID) injections (Supplemental Content 2, Figure 1).

Hours later, he called our clinic to report, having forgotten to ask why nothing was injected into the wound. To remind him about next steps, he was e-mailed a copy of CDC's recommendations on rabies PEP [2].

Despite canine rabies in Bhutan [24] and a WHO category III (severe) exposure (9), RIG had not been offered nor was capturing the dog possible. Since this traveler could revise his trip, we directed him to his next stop, Bangkok, after first identifying via e-mails a hospital-based clinic offering RIG-containing PEP. In Bangkok, 3 days after the bite, HRIG (20 IU/kg) was injected entirely in and around the wound and an initial (day 0) IM injection of Verorab™ was given in the deltoid (Supplemental Content 2, Figure 2); additional vaccine doses were injected IM on days 3 and 7. On return home (day 14), he received a final IM injection (Imovax™) in our clinic. The bite site had healed, and he has remained entirely healthy.

Case analysis

Patient 3's vaccine injections in Bhutan were given ID, a route commonly used in endemic regions but not approved in the U.S. since 2001 (and then only for PrEP). WHO considers ID-administered rabies vaccine (Table 3) as effective as IM injection protocols [9], and while there is renewed interest in the U.S. [25,26], ID injection protocols remain unfamiliar to most U.S. clinicians. Nonetheless, the failure to give RIG (not unusual in Bhutan [27]), not the use of an established ID injection protocol, led us to advise Patient 3 to revise his trip in favor of Bangkok. We also knew that the administered vaccine in Bhutan could not be identified, from his itinerary that PEP could be completed in NYC and that the Bangkok clinic would provide HRIG and IM injections of a WHO pre-qualified vaccine (Verorab™). Supplemental Content 2's figures illustrate Patient 3's rabies-specific information, transmitted in real-time and particularly helpful in decision-making. Such data should be requested from travelers receiving rabies PEP abroad.

Patient 4

In 2018, the wife of a healthy 69-year-old man e-mailed our clinic from a cruise ship off Indonesia requesting advice about rabies PEP. Three days before, her husband was bitten on the hand by a macaque monkey in the Ubud Monkey Forest Park on Bali. In the park's first-aid station, the wound was briefly wiped, a dressing applied, and he was told that "monkeys on Bali do not have rabies" and that no further care was necessary. He thus did not seek medical care after returning to the ship. Via e-mail, our clinic's advice included (a) that he needed wound examination in the ship's medical unit with extensive cleansing if the wound was still open (it was not), (b) prophylaxis against rabies (and possibly herpes B virus infection [12]), and (c) if such care was not available to consider repatriation as his trip was soon to end. He had had a tetanus toxoid booster 1 month before travel.

Two days later (5 days after the bite), he returned to New Jersey, and the next morning, saw his physician who concluded that the closed wound did not warrant antibiotic therapy. He was referred to

an Infectious Diseases consultant who could not see him for 4 days. After 3 anxious days of waiting, he saw another consultant who immediately sent him to a local emergency department for rabies PEP. After discussion, the consultant also prescribed valacyclovir (1 g thrice-daily for 14 days) as herpes B prophylaxis [11,12]. HRIG (20 IU/kg) was injected in and around the hand wound as anatomically feasible, the residual HRIG volume was given IM into one deltoid and rabies vaccine (Imovax™) was injected into the other. He was given 3 additional vaccine injections 3, 7 and 14 days later, and completed valacyclovir prophylaxis. He kept our clinic informed of the preceding interventions, and reported an uneventful recovery.

Case analysis. Patient 4's wife showed well-founded concern, and sought guidance once she recognized that initial wound care and medical advice in the monkey park was inadequate and PEP was not available on the cruise ship. Beginning rabies PEP 9 days after the bite would not be considered prompt; once evaluated at home and with a same-day telephone consultation (Table 4), PEP could have been started earlier. PEP against herpes B, which causes rare but often fatal infection [12], reflected abundant caution for a perceived high-risk exposure (rhesus macaque, poorly-cleansed bite wound) [11,12]. Whether PEP for herpes B infection (incubation period usually 5-21 days, range 2-35 days [28]) was actually warranted, however, is less certain—thousands of macaque bites likely occur every year in visitors at temples and monkey parks in South and SE Asia, yet herpes B infection has not been reported in a traveler [12].

Discussion

Animals of concern

Patient 1 was bitten by a fox. Any mammal can be infected with rabies virus and theoretically transmit infection to humans via saliva or neural tissue [2,9]. Airborne (aerosol) transmission (e.g., to travelers exploring caves crowded with *Lyssavirus*-infected bats) has very rarely been implicated [9]. In 83 cases of imported rabies in travelers and migrants (1990-2019), involved animals were dogs (91%), cats, raccoons and foxes (5%) and bats (4%) [6,7]. Table 2 lists other wildlife of concern, possible concern or no concern for transmitting rabies.

Animal exposures in travelers

Dogs appear responsible for up to 99% of rabies virus transmission to humans in endemic regions [9]. However, in international travelers with bite and nonbite at-risk exposures, the range of animals of concern is considerably more broad -- dogs (48-67%), cats (12-29%), monkeys (17-32%) and bats (1-2%) (1,29-31); similar breadth occurs in those seen for nonbite exposures only -- monkeys (40%), dogs (27%), cats (22%), other animals (6%) and bats (5%) [30]. Worldwide, but with regional exceptions [24], bat contact is considered a *Lyssavirus* exposure and thus a rabies risk.

Country of exposure and its current rabies status

Patient 1's 2009 fox attack occurred in Italy, free of rabies virus in terrestrial animals since 1997 until an outbreak in foxes in the

northeast in 2008-2011 (Italy was re-certified rabies virus-free in 2013). Worldwide (see Supplemental Content 1D for regional data), leading countries of exposure to rabies in travelers vary by report: (a) India, Philippines, Morocco/Algeria and Mexico in cases of imported rabies (1990-2019) [6,7], and (b) Thailand, Indonesia, Nepal, Vietnam and Cambodia as well as India and China in travelers who received PEP during 2007-2019 [29-31]. Leading countries also vary depending on exposure (bite vs. nonbite) and involved animal [29].

Immediately available country information helps in judging an exposure's potential as a rabies risk. CDC's on-line search tool (Table 4) provides worldwide, country-specific information on the status of rabies in dogs, terrestrial wildlife and bats [24]. Importantly, the same tool also scores country-by-country the availability (available, limited or none) of high-quality rabies vaccines and RIG.

Vaccine interchangeability

Had completion of Patients 2's already-initiated PEP been warranted, a different type of cell-derived vaccine would necessarily have been used -- Imovax™ (a human diploid cell vaccine (HDCV)) or RabAvert™ (a PCECV), the vaccines available in the U.S. While considered ideal to complete a series with the same vaccine, practicality rules and, despite little actual supporting data (32), cell-derived vaccines are considered interchangeable; no case of rabies in the U.S. has been attributed to using a different vaccine to complete PEP. Thus, once a vaccine series begun abroad has been determined satisfactory (type and tradename; number and timing of injections (Tables 3 and 5)), it can be completed with either Imovax™ or RabAvert™. If any doubt exists, including about the initial vaccine's quality or injection protocol, consultation is warranted and the traveler's antibody response can be verified 2-4 weeks after undertaking completion of the series (see Supplemental Content 1E) [33].

Interchangeability of route of vaccine administration

Considerable heterogeneity exists in PEP regimens in endemic countries, particularly in Asia [34]. Thus, travelers like patient 3 who begin PEP overseas may well receive initial vaccine doses by ID injection; completing PEP in the U.S. would necessarily require the IM route. A limited study from India indicates that early in a PEP protocol ID- and IM-administered cell-derived rabies vaccine is interchangeable [32], and, in the U.S., human rabies has not been attributed to a change in PEP from ID- to IM-administered vaccine. Conforming to WHO recommendations [35], guidelines in Australia (where ID-administered vaccine is also not registered) indicate that for returning travelers in whom PEP completion is warranted clinicians can align with the nearest injection due date and resume the PEP schedule with IM vaccine [36]. Conditions to be met also include an immunocompetent traveler in whom RIG was given before day 7 and clear documentation about the vaccine and its administration [36].

Failure to administer RIG

Just as in patients 2 and 3, the majority (64-96%) of travelers in rabies endemic regions in whom RIG is indicated by WHO criteria [9,16] do not receive it as part of their PEP in the exposure country [29]. Even though WHO limits RIG use to begin with to select exposures (Category III [9], Table 3), < 2% of those in whom RIG (HRIG or equine RIG) is warranted actually receive it worldwide [9]. At the same time, WHO also maintains that 99% of cases of rabies can be prevented without RIG by thorough wound washing and prompt, complete vaccination [9]. See Supplemental Content 1F for reasons why RIG is not administered.

Monkey bites and rabies risk

About one-third of injuries (range, 8-69%) for which travelers seek rabies PEP stem from nonhuman primate (NHP) exposures [37], mainly in India, Nepal, Indonesia and Thailand. Like Patient 4, up to an estimated 6% of visitors to Bali's monkey temples or parks may be bitten by macaques [38]. Yet, while little is known about rabies in macaques and other NHPs, at least 25 human cases have resulted from such exposures, primarily from marmoset bites and mostly in Brazil [37,38]. Nevertheless, while the risk of transmitting rabies is considered extremely low (WHO no longer formally lists monkeys as an animal of concern [9,16,19]) and expert opinion and national guidelines vary widely [37,39], PEP must be considered if the bite occurred in a rabies-enzootic country.

What is prompt rabies PEP?

Patient 4 started PEP 9 days after his bite. In the majority of human rabies cases, the incubation period (exposure to clinical disease onset) is long at 30-90 days [9,16], and has been subdivided as < 30 days in 25%, 30-90 days in 50% and 90 days-1 year in 20% of cases [22]. In imported human rabies, median incubation periods have been recorded at 56-80 days [6,7]. At the same time, fulminant disease (incubation period \leq 7 days) may sometimes follow severe bites in particular to the head, face and neck [23,40]; bites at these locations always need immediate action. In most other settings in which PEP is warranted, however, there is no firm definition of "prompt" or "immediate" (other than as soon as possible). Recent reports from Europe used \geq 24 hours after exposure to define delayed PEP [31] and HRIG given in < 48 hours and starting vaccination within 7 days to define timely PEP [39].

Conclusions

Albeit infrequent, clinicians in the U.S. may be called upon to (a) provide initial basic guidance to a traveler abroad with a rabies at-risk exposure, and/or (b) promptly recognize the need for and how to access expert advice. Once the potentially complex decision is made that rabies postexposure rabies prophylaxis – wound care, immune globulin injection and vaccine – is warranted, the clinician's role is to oversee its proper completion without delay.

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Supplemental Content 1

A. Late-appearing traveler with an untreated rabies exposure

While infrequent, clinicians in the U.S. may also encounter an international traveler who many months (or even years) before experienced a bona fide rabies at-risk exposure abroad, failed to recognize and/or report it and has not received PEP. Rabies virus can persist long-term in human tissue, and although considered rare, > 1 year (or even longer) may elapse between exposure and neurologic disease onset (1,2). The published estimated likelihoods of long incubation periods in human rabies vary: > 6 months in 1-10%, 90 days to 1 year in 20%, and > 1 year in 1-5% of cases (3-5). Nevertheless, it is well to recall that PEP can be given at any time after an exposure, albeit probably with less efficacy as time passes (6). Thus, and with expert guidance (Table 4), full PEP including HRIG injected into the now-healed original site may well be indicated in such a late-appearance setting.

B. Risk factors: unprovoked bite and animal's vaccination status

Patient 2's bite in India was unprovoked (not feeding or handling), and the dog had reportedly been vaccinated against rabies. Unprovoked exposures occur in 25-30% of travelers (7,8), and heighten the possibility that the animal is rabid. However, the circumstances of the bite should mostly be disregarded, especially in rabies-endemic countries such as India, and not used in deciding about PEP (3,9). As a rule, the same conclusion applies to the biting animal's reported vaccination status (3,9-11). Although properly and "currently" vaccinated animals are unlikely to acquire rabies, vaccination failures may occur in dogs (even in the U.S.) despite the use of conventional veterinary vaccines (10,11).

C. Initially withholding PEP and the 10-day quarantine period

PEP can be initially withheld if the at-risk bite is from a healthy-appearing dog/puppy, cat/kitten or ferret if it can be formally confined and reliably observed to remain healthy for > 10 days. The same guideline could also apply to a healthy-appearing stray (dog, cat or ferret) if captured; however, it does not apply to other biting terrestrial mammals, any highly-suspect animal or to bats. Similarly, if PEP has been started and the confined animal remains healthy for > 10 days (or its brain tissue tests negative, if euthanized), remaining injections can be discontinued as in Patient 2. The clinical usefulness of the 10-day observation (quarantine) period is well-established (12). Nevertheless, too many factors would have to converge successfully in endemic regions to likely make such an observation period either relevant to or practical for a bitten traveler, especially one on a fixed itinerary (8).

D. Regions of exposure in travelers

In cases of imported rabies (2,13) and GeoSentinel surveys of travelers who initiated PEP abroad or after return (7,14), Asia was the leading region of exposure (57-76%), followed by Africa (10-28%) and South/Central America and the Caribbean (8-13%); in Asia, Southeast Asia ranked highest (47-79%) (7,14). The actual regional incidence of rabies at-risk exposures in returning travelers, however, shows more uniformity -- Asia at 2.3% exposures per trip, followed by South-Central America (1.9%), the Caribbean (1.7%), Africa (1.6%) and the Middle East (0.8%) (8).

E. Serologic testing for anti-rabies antibody

In immunocompetent individuals who receive PEP entirely in the U.S., verifying the anti-rabies virus antibody response 2-4 weeks after PEP completion is not indicated (15). This conclusion does not apply to the immunocompromised host (15), however, nor to travelers in the following settings in which a suboptimal titer would indicate the need for additional vaccine or possibly even restarting a vaccine series: (a) RIG not given, of questionable quality or given > 7 days after the day 0 vaccine dose, (b) equine RIG or anti-rabies monoclonal antibody used, (c) suspect vaccine quality, handling or storage, (d) appreciable deviation from an accepted vaccine schedule, and being cautious, (e) having completed PEP entirely in a resource-limited region (16-19). In Patient 3, we reasoned that having received documented HRIG and a recognized vaccine on an accepted schedule abroad (with the final vaccine dose in the U.S.), he could

forgo serologic testing to verify an adequate antibody response. The rapid fluorescent focus inhibition test, which titers complete rabies virus neutralization, is considered the gold standard serological assay, not ELISA testing for antibody (17).

F. Failure to administer RIG

RIG is injected to provide immediately-acting, neutralizing antibody at the site of rabies virus inoculation. The reasons why RIG is not often administered in endemic regions revolve around chronic worldwide problems – high cost, limited (or no) national or local availability, short shelf half-life and, like vaccine, refrigeration requirements (7,19). Insufficient awareness of the need or indications for RIG on the part of medical providers and reluctance to perform the injections are also recognized (7,19,20). Potential drawbacks to RIG's use include improper injection technique, batch-to-batch variation and uncertain quality which could affect efficacy (no RIG preparation is WHO pre-qualified) (21).

In response to the preceding problems and as an alternative to RIG, WHO supports the development of anti-rabies monoclonal antibody products containing more than one antibody (1,22). Results from a recent, randomized phase 3 trial in India indicated that one such a monoclonal antibody cocktail (Twinrab™) was safe and noninferior to HRIG in the PEP protocol administered to adults with WHO Category III exposures from suspected rabid dogs (23).

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Supplemental Content 2

Figures 1 and 2: Rabies Exposures in International Travelers (Henry W. Murray, M.D.).



Figure 1: Information e-mailed from Bhutan by Patient 3 on the day of the dog bite (October 28, 2015). (Left) Bite on back of right thigh. (Right) Medical documentation of clinic examination, care rendered, 2-site vaccine injection on day 0 (28/10/15) and 2-site injection vaccination schedule for days 3, 7 and 28.

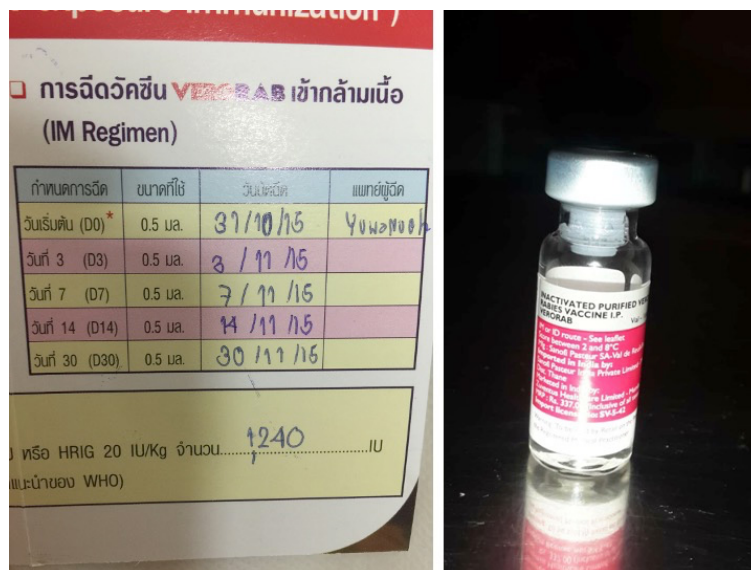


Figure 2: Information e-mailed by patient 3 from Bangkok on arrival on October 31, 2015 at initial clinic visit. (Left) Documentation of HRIG and IM vaccine administered on 31/10/15 and schedule for subsequent IM vaccine injections. (Right) Vaccine administered.

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