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Epidemiology of rabies cases among international travellers, 2013-2019: a retrospective analysis of published reports

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Abstract

Background: Sixty cases of rabies in international travellers from 1990-2012 were previously reviewed. We present here an update of rabies cases in international travellers from 2013-2019.

Methods: We systematically reviewed the existing literature and collected 23 cases of rabies in individuals who crossed an international border between the time of infection and diagnosis, or who were infected following expatriation or migration.

Results: Most cases were in male adult travellers and diagnosed in Europe and the Middle East, with most exposures in Asia or in Africa. Migrants originating from rabies-endemic low-and-middle income countries and their descendants accounted for two thirds of cases. Other cases were in tourists, business travellers and expatriates. Median travel duration (excluding migration trip) was 60 days (range 7-240 days). Most cases were due to dog bites and most common clinical presentation was furious rabies. In most patients (74%), no rabies post-exposure prophylaxis (RPEP) was administered before rabies symptoms appeared. Other patients received incomplete RPEP series.

Conclusion: Rabies should be suspected in any patient with encephalitis or paralysis who travelled to, or migrated from a rabies-endemic country. Comprehensive information about a rabies risk should be given to travellers to rabies endemic countries, notably migrants visiting friends and relatives.

Key words

Rabies; Traveller; Imported; Epidemiology; Diagnosis

Introduction

Rabies in international travellers is a rare but dramatic deadly event that usually leads to case reporting in the medical literature [1] and frequently receives media attention. A previous review for the period 1990–2012 using the PubMed and Scopus search engines, and reviewing ProMED-mail, revealed 60 cases of travel-associated rabies (2-3 cases per year) worldwide [2]. Most cases were diagnosed in Europe and in the United States of America (USA). Most exposures occurred in Asia (24/40; 40%), notably in India and the Philippines; in Central America and the Caribbean (9/60, 15%); and in North Africa (6/60, 10%). A significant proportion of cases occurred in migrants or their descendants (26/60; 43%). They were infected in their origin country prior to migration (7/26; 27%), or infected during a trip to their origin country for the purpose of visiting friends and relatives (14/26; 54%), or for other reasons (5/26; 19%), whilst the remaining cases were in individuals travelling for tourism, business or expatriation (34/60; 57%). Travel duration was not documented in the majority of the reports. Two cases were recorded in tourists taking two-week trips to India and Kenya. A predominance of male patients was observed (45/60; 75%) and the proportion of adults was high (50/57; 88%). Dogs were involved in most cases (51/55; 93%), bats in three cases and a fox in one case. In half of the cases, the diagnosis was challenging, with multiple missed diagnoses and transfers from specialty to specialty before the diagnosis of rabies was confirmed. In one-third of the cases a confirmed diagnosis of rabies was obtained only *post-mortem*. This was mostly due to a low index of suspicion for rabies from physicians lacking familiarity with the disease, a negative history of animal bites or exposure to rabies, and atypical clinical presentation of the disease.

We present here an update of rabies cases in international travellers from 2013 to 2019.

Materials and Methods

We retrieved information on human rabies cases in travellers using PubMed (MEDLINE) and Scopus databases (http://www.ncbi.nlm.nih.gov/pubmed; www.scopus.com/scopus/home.url), from January 2013 to December 2019, cross-referencing the following terms: 'rabies', 'imported' and 'travel'. Additionally, we searched the two databases for all rabies case reports and checked for possible travel association. The reference lists of the systematic reviews and other identified papers were scanned for potentially relevant primary studies that could be considered for inclusion in the review. Additional searches were conducted using the ProMED-mail (http://www.promedmail.org/) and Google (http://www.google.fr/) general search engine. Finally, the GeoSentinel/EuroTravNet (https://www.istm.org/geosentinel - https://www.istm.org/eurotravnet) database was queried for potentially relevant cases.

The inclusion criteria were all available publications written in English, French and Spanish languages on human rabies cases in individuals who crossed an international border between the time of infection and diagnosis or who were infected following expatriation or migration. Reports with insufficient clinical descriptions were only included in the epidemiological analyses. When possible, corresponding authors of case reports and public health representatives were queried for missing information. We used WHO guide as a standard for rabies prophylaxis (https://www.who.int/rabies/PEP_Prophylaxis_guideline_15_12_2014.pdf).

Results

Epidemiology (Tables 1,2)

A total of 23 cases meeting the inclusion criteria were identified from 2013 through 2019 [3-25], an average of three cases per year over the seven-year study period, with a maximum of six cases in 2014. One 2019 case in a Latvian citizen, where country of acquisition was unascertainable (Latvia or India) was excluded. The mean age of patients was 36 years (range, 4-65 years). Three cases were reported in children, including a 12 year-old Yemeni refugee who was infected in Saudi Arabia [16], a 10 year-old French tourist child infected in Sri-Lanka and a 3 year-old Zimbabwean migrant to South-Africa, infected in Zimbabwe [18]. The male-to-female ratio was 2.8. Most cases were diagnosed in Europe (10/23, 44%), notably in France (3 cases), in The Netherlands (2 cases) and in Spain (2 cases), and the Middle East (6/23, 26%); notably in Saudi Arabia (2 cases) and in Qatar (2 cases). Migrants originating from rabies-endemic low-and-middle income countries and their descendants accounted for 61% (14/21) of cases, following initial migration trips (8 cases) or when visiting friends and relatives in their country of origin (6 cases). Other individuals were from developed countries and acquired rabies when travelling for tourism (6 cases), business (2 cases), and expatriation (1 case). Most exposures occurred in Asia (13/23, 57%) (Figure 1), notably in India (5 cases) and Philippines (3 cases), or in Africa (7/23, 30%), notably in Morocco (4 cases). Additionally, there were two cases with exposure in Central America and one in Saudi Arabia. Travel duration (excluding migration trip) was documented in 9/15 cases. Median travel duration was 60 days (range from 7-240 days). Of note, a Dutch citizen travelled for one week, in Haiti for business purpose [3] and a Saudi citizen travelled for 12 days in Morocco for tourism [17]. A history of an animal bite or scratch was reported in 20/23 cases and involved dogs in 17 cases; with two cases resulting from cat bites in Morocco and one case resulting from the bite of a raccoon-like animal in Nepal. In three patients, no animal-related injury was reported, but one patient owned a dog in Guatemala, which died of unknown cause [5], and another patient had stray dogs in his residency area. In a case from

Mali, phylogenetic analysis based on the full-length viral nucleoprotein nucleotide sequence indicated that the virus isolate belonged to the Africa 2 phyloclade within the *Rabies lyssavirus* (RABV) species, which is known to circulate dogs in West Africa [7].

Four secondary cases (not travel-associated) were observed in transplant recipients from Kuwait and Saudi Arabia who received organs (heart, liver, kidneys) from an Indian migrant worker donor diseased in Kuwait. Additionally, two cornea recipients from the same donor underwent explantation and survived [14,15].

Clinical features and biological confirmation of rabies

The incubation time was documented in 19/23 cases (Figure 2) with a mean incubation time of 87.6 days (median time: 56 days, range, 30-420). The longest incubation time was about 14 months in a Czech patient who sustained a dog bite in Bangladesh while travelling for tourism and developed rabies disease during a stay in France. In 14 reports, the clinical description was adequate to allow classification of the disease. Thirteen cases were furious rabies and one paralytic. Hydrophobia was reported in 7 cases, hypersalivation in 5 cases and aerophobia in 3 cases.

Atypical presentations included a case of severe alkalosis due to hyperventilation with ketonuria and hyperglycemia, as initial presentation [7]. Another patient presented with an acute myocarditis (a common feature in rabies) but with electrocardiogram changes (ST elevation) initially interpreted as suggestive for myocardial infarction [20]. One patient was initially misdiagnosed with sepsis [11]. One patient presented with a pneumomediastinum [5], and the single paralytic case was initially misdiagnosed as Guillain-Barré syndrome [10]. In the majority of cases with available information, diagnosis was made by PCR on skin biopsy

or saliva and CSF. Unfortunately, information about the variant types of lyssavirus was lacking in most reports.

In 17 patients (74%), no rabies post-exposure prophylaxis (RPEP) was administered before rabies symptoms appeared. In two cases, no RPEP was mentioned. The remaining four cases reportedly received incomplete RPEP series. One patient from the Netherlands had supposedly received four doses of vaccine in India the next day after sustaining a transdermal bite in her hand, but proof of vaccination was lacking and the vaccination schedule was deviant from any international RPEP guideline (4 vaccinations in a time period of 2 weeks). Possibly, counterfeit vaccine was administered [26], given the fact that serum antibodies against rabies virus were low (<0.5 IU/ml), measured at diagnosis, eight weeks later. This patient did not receive rabies immune globulin (RIG) and developed rabies symptoms eight weeks after exposure [8]. The French patient expatriated to Cambodia received one dose of a vaccine following a transdermal bite in her hand, according to a witness, (could not identify whether that one dose was rabies or tetanus vaccine) but no RIG in Cambodia, and developed rabies eight months later [12]. The Zimbabwean patient received one dose of confirmed rabies vaccine in Zimbabwe and another in Tanzania following a transdermal bite in his neck but no RIG, according to family and developed rabies 79 days later. Finally, the Italian patient received rabies vaccines in Tanzania (number of doses not documented in the report) but no RIG and developed rabies one month later [24]. The type of injury was not described in this last case. Information about treatment in symptomatic patients was missing in most cases; however, a treatment attempt based on the Milwaukee protocol [27] (or derived from), that includes therapeutic coma, ketamine infusion, amantadine, and the screening/prophylaxis/management of cerebral vasospasm was conducted in six patients [5,10,11,15,16,19]. All 23 patients died.

Discussion

This update shows that rabies cases among travellers continue to occur with no significant change as compared to the period 1990–2012 regarding the absolute number of cases. Although likely underestimating the true burden of rabies among international travellers and migrants, notably in patients travelling between developing countries, this figure of three cases per year stands in marked contrast with the estimated 0.4% per-month incidence of animal bites requiring RPEP in international travellers that was calculated from prospective cohort survey data conducted among travellers enrolled prior departure and questioned on return [28]. Risk factors cannot be extrapolated from our results because we lack denominators. Of note, only three patients definitely received some fraction of RPEP of whom one only had received a complete course of vaccine, and none had received RIG. RPEP might be difficult to obtain in some countries during travel, notably RIG and in the event that it is obtained, it can be counterfeit [26]. In a recent GeoSentinel survey, about two-thirds of travellers with an indication for RIG who started RPEP while travelling did not receive RIG [29]. The death of the three patients in our series is not indicative of failure of RPEP since vaccine courses were incomplete and RIG was missing despite being indicated due to the nature of injuries in at least two cases.

Similar to the previous period of 1990-2012, a predominance of adults and male patients was observed in travellers with rabies. Unlike in populations living in rabies-endemic countries where children < 15years represent a large portion of human rabies cases (40-50%) [30], children were under-represented in this study (8%) as well as in the previous one (11%) [2]. This correlates with data on potentially rabid animal exposure in travellers seeking care for RPEP, as observed in a large GeoSentinel survey where children under 15 years accounted for 11% of patients [31]. This may be due to the age profile of travellers which is different from the age profile in those countries were rabies is most highly endemic. By contrast, the

predominance of male patients with rabies (74%), in our study and in the previous one (75%) [2], does not correlate with the 51% male patient proportion observed in the GeoSentinel survey on travellers seeking care for RPEP [31]. Europe remained the commonest region where cases are diagnosed which is likely reflecting both the quality of rabies surveillance and the large numbers of tourists and migrants from and to Europe. The Middle-East region emerged as second with reports from Qatar, Kuwait, Saudi Arabia and Israel. Of note, there was no recent case acquired in Mexico, a country from which 5 cases were acquired between 1990-2012, with the last one in 2010 [2]. This might be chance, but most likely rather reflects the success of Mexico's canine rabies elimination efforts and their newly recognised status by the World Health Organization as "free from dog-mediated human rabies deaths" [32]. Migrants from low-income countries accounted for most of the recent cases; in contrast with the previous data from 1990-2012, where travellers from high-income countries accounted for the majority of cases. This may be possibly due to increased rabies prevention among travellers. India, the Philippines and Morocco continue to be the top countries for exposure. In a GeoSentinel study about patients receiving RPEP, most exposures occurred in Asia (74%) with top countries being Thailand, Indonesia, Nepal, China and India, and only 5% in North Africa [31]. New countries of acquisition emerged, including Saudi Arabia, Indonesia, Cambodia, Zimbabwe, Tanzania (Zanzibar) and Guatemala (Figure 1). As observed previously [2], the diagnosis was challenging in some cases, because of atypical presentation and because a history of animal bite or exposure to rabies was lacking. In one migrant from India to Kuwait, the diagnosis was missed, resulting in subsequent cases in four organ recipients [14,15]. A similar scenario occurred in Germany in 2005, with three cases of rabies in patients who received transplants from a donor that was retrospectively diagnosed with rabies resulting from a dog bite in India that was not known at the time he died [33]. This

suggests that history of animal bites in a rabies endemic country should be queried before donation.

Understandably, physicians in countries where rabies has been eliminated many years ago are not familiar with rabies symptoms. A history of an animal bite is frequently missing, incubation time may be long and symptoms may be atypical. Despite the rarity of human rabies deaths in many high-income countries, rabies should be suspected in any patient with encephalitis or paralysis who travelled to or migrated from a rabies endemic country [2].

Comprehensive information about a rabies risk should be given to travellers to rabies endemic countries, notably migrants visiting friends and relatives. As it conveys life-long boostability, pre-travel vaccination which has been recently simplified from three doses over one month to two doses over one week [34] should be considered, and not only to long-term travelers since the median duration of travel was 15 days in patients seeking care for RPEP after travel and 20 days in those seeking care during travel, in the GeoSentinel survey [31] and the median time between departure from home and occurrence of exposure to a potentially rabid animal was nine days in a Dutch study conducted among patients seeking care for RPEP on return to the Netherlands [35]. This shortened rabies pre-travel vaccination two-dose schedule, and the use of the intra-dermal route that allows reducing the amount of compound needed [36] makes pre-travel vaccination easier and cheaper [37,38]. Easier access to rabies pre-travel vaccination is of major importance given that animal exposure in international travelers can happen anywhere on almost any continents, including in countries endemic for rabies as recently demonstrated in an updated GeoSentinel survey [39].

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Figure legends

Figure 1. Country of exposure in 83 travel-associated rabies cases (black numbers: 1990-2012, red numbers: 2013-2019).

Figure 2. Incubation time (19 human rabies cases in travellers (2013–2019). Logarithmic scale. Each circle represents one patient. Case numbers corresponding to Table 1 are indicated underneath along the horizontal axis.

Table 1. Characteristics of 23 travel-associated rabies cases (2013-2019)

Case	Year	Country of exposure	Country where the diagnosis was established	Country of origin	History of animal exposure	RPEP before symptoms	Gender, age (years)	Reason for travel	Travel duration	Incubation period	Clinical symptoms	Positive samples for rabies virus (PCR and or culture) or antibodies	Lyssavirus species	References
1	2013	Haiti	The Netherlands	The Netherlands	Dog bite	No	Male, 52	Business	1 weeks	34 days	Fever, headaches, malaise, arm, shoulder and trunk pain and dysaesthesia, hydrophobia	Skin biopsy, CSF, saliva (virus)	*Rabies lyssavirus* (RABV)	[3]
2	2013	Philippines	Taiwan	Philippines	Dog bite	No	Male, 31	Migration (worker)	Not applicable	55 days	Hand pain, nausea, vomiting, anorexia, sore throat, fever, conscious disturbance, fatigue, unsteady gait and hand twitches, slurred speech	Not described	-	[4]
3	2013	Guatemala	US, Texas	Guatemala	None reported (owed a dog in Guatemala which died from unknown cause in 2011	No	Male, 28	Migration (illegal)	Not applicable	Not ascertainable	Insomnia, anxiety, nausea, dysphagia, hypersalivation and expectoration, agitation, tachycardia, chest pneumomediastinum, fever, aerophobia	Skin, brain, saliva (virus) and Serum, CSF (antibodies)	*Rabies lyssavirus* (RABV)	[5]
4	2014	Indonesia	China (Hong Kong)	Indonesia	Dog bite	None reported	Male, 28	Business	Not documented	About 2 months	Back and loin pain, fever, vomiting, walking difficulties	Brain (virus)	Not documented	[6]
5	2014	Mali	France	Mali	None reported (stray dogs in his residency area)	No	Male, 57	VFR	6 months	Not ascertainable (2 weeks to 6 months)	Fever, sweating, generalized pain, anxiety, tachypnea, hyperactivity, disorientation, delirium, periods of drowsiness, hypersalivation, evolution toward rapidly extensive flaccid and non-reflexive tetraparesis	Skin, saliva, bronchial secretions (virus) and serum (antibodies)	*Rabies lyssavirus* (RABV)	[7]
6	2014	India	The Netherlands	India	Dog bite	Yes (4 rabies vaccine injections in India, no RIG)	Female, 35	Migration (married a Dutch citizen)	Not applicable	8 weeks	Hand, arm and neck pain, hydrophobia, aerophobia, anxiety	Skin, CSF, saliva (virus)	*Rabies lyssavirus* (RABV)	[8]
7	2014	Morocco	Spain	Morocco	Dog bite	No	Female, 46	VFR	4 months	7 months	Fever, foot pain and paresthesia, anxiety, dysphagia for liquids, delirium	Skin, saliva (virus)	Not documented	[9]*
8	2014	India	Israel	India	None reported	None reported	Female, 32	Migration (worker)	Not applicable	Not ascertainable	Emotional instability, anxiety, agitation, sore throat, abdominal pain, vomiting, diarrhea, leg weakness, fever, diffuse muscle pain, dizziness, back and neck pain, tachycardia, dyspnea, generalised areflexia and hypotonia, trismus, evolution toward paralysis of the four limbs.	Skin, saliva (virus)	*Rabies lyssavirus* (RABV)	[10]
9	2014	India	Qatar	India	Dog bite	No	Male, 26	VFR	Not documented	1 month	Dyspnea, tight pain, dysuria, anxiety, tachycardia, tachypnea,	Only CSF antibodies were search and resulted negative. Diagnostic was based on clinic and epidemiological context	-	[11]

10	2015	Bangladesh	France	Czech Republic	Dog bite	No	Male, 41	Tourism	Not documented	14 months	Not documented	Saliva and brain (virus)	*Rabies lyssavirus* (RABV)	**
11	2015	Cambodia	Cambodia	France	Dog bite	Unclear (one dose of vaccine – rabies or tetanus in Cambodia, no RIG)	Female, 25	Expatriate	8 months	About 50 days	Fever, pharyngeal spasms preventing hydration, diarrhea, vomiting, hypersalivation, hydrophobia	Saliva (virus)	*Rabies lyssavirus* (RABV)	[12]
12	2015	Philippines	US, Massachusetts	Philippines	Dog bite	No	Male, 65	VFR	5 months	36 days	Severe gastro-intestinal symptoms, dysphagia, respiratory failure	Skin (virus), CSF (antibodies)	*Rabies lyssavirus* (RABV)	[13]
13	2015	India	Kuwait	India	Dog bite	No	Male, 28	Migration (worker)	Not applicable	2 months	Seizure, chest infection and cardiac arrest	Diagnostic was made in transplant recipients.	Not documented	[14,15]
14	2016	Saudi Arabia	Saudi Arabia	Yemen	Dog bite	No	Male, 12	Migration (refugee)	Not applicable	38 days	Agitation, delirium, insomnia, dehydration, aerophobia, hydrophobia, fever, tachycardia,	Saliva (virus)	Not documented	[16]
15	2016	Morocco	Saudi Arabia	Saudi Arabia	Dog scratch	No	Male, 60	Tourism	12 days	1 month	Nausea, vomiting, epigastric pain, chest tightness, dyspnea, tachycardia, chest pain, hydrophobia,	Saliva(virus)	Not documented	[17]
16	2017	Sri-Lanka	France	France	Dog bite	No	Male, 10	Tourism	3 weeks	1 month and half	Not documented	Skin, saliva (virus)	*Rabies lyssavirus* (RABV)	**
17	2017	Zimbabwe	South Africa	Zimbabwe	Dog bite	Yes (one dose of rabies vaccine in Zimbabwe and one dose in Mozambique, no RIG)	Male, 3	Migration (joined his father who is a migrant worker)	Not applicable	79 days	Aggressive behavior, confusion, agitation, fever, vomiting, hypersalivation, headaches, seizures	Saliva (virus)	Not documented	[18]***
18	2017	India	US, Virginia	US	Dog bite	No	Female, 65	Tourism	5 weeks	6 weeks	Arm pain and paresthesia, dyspnea, anxiety, agitation, insomnia, difficulty in swallowing, claustrophobia, tachycardia, dysmetria, hydrophobia, fever, myocarditis	Skin, saliva (virus)	*Rabies lyssavirus* (RABV)	[19,20]
19	2018	Morocco	UK	Morocco	Cat bite	No	Male, 58	VFR	Not documented	Not documented	Not documented	Not documented	Not documented	[21]
20	2019	Nepal	Qatar	Nepal	Raccoon-like animal bite (possibly red panda)	No	Male, 26	Migration (worker)	Not applicable	6 months	Hydrophobia, lake of consciousness and neurological symptoms (not described)	Not reported	Not documented	[22]
21	2019	Philippines	Norway	Norway	Dog bite	No	Female, 24	Tourism	2 months	About 3 months	Not described	Not described	Not documented	[23]
22	2019	Zanzibar, Tanzania	Italy	Italy	Dog bite	Received vaccines (undocumented number), no RIG	Male, 44	Tourism	Not documented	1 month	Not described	Not described		[24]
23	2019	Morocco	Spain	Morocco	Cat bite	No	Male, middle age	VFR	Not documented	4 months	Necrosis of the bite area, nausea, confusion, dysarthria, coma	Skin, saliva (virus)	Not documented	[25]*

VFR: visiting friends and relatives

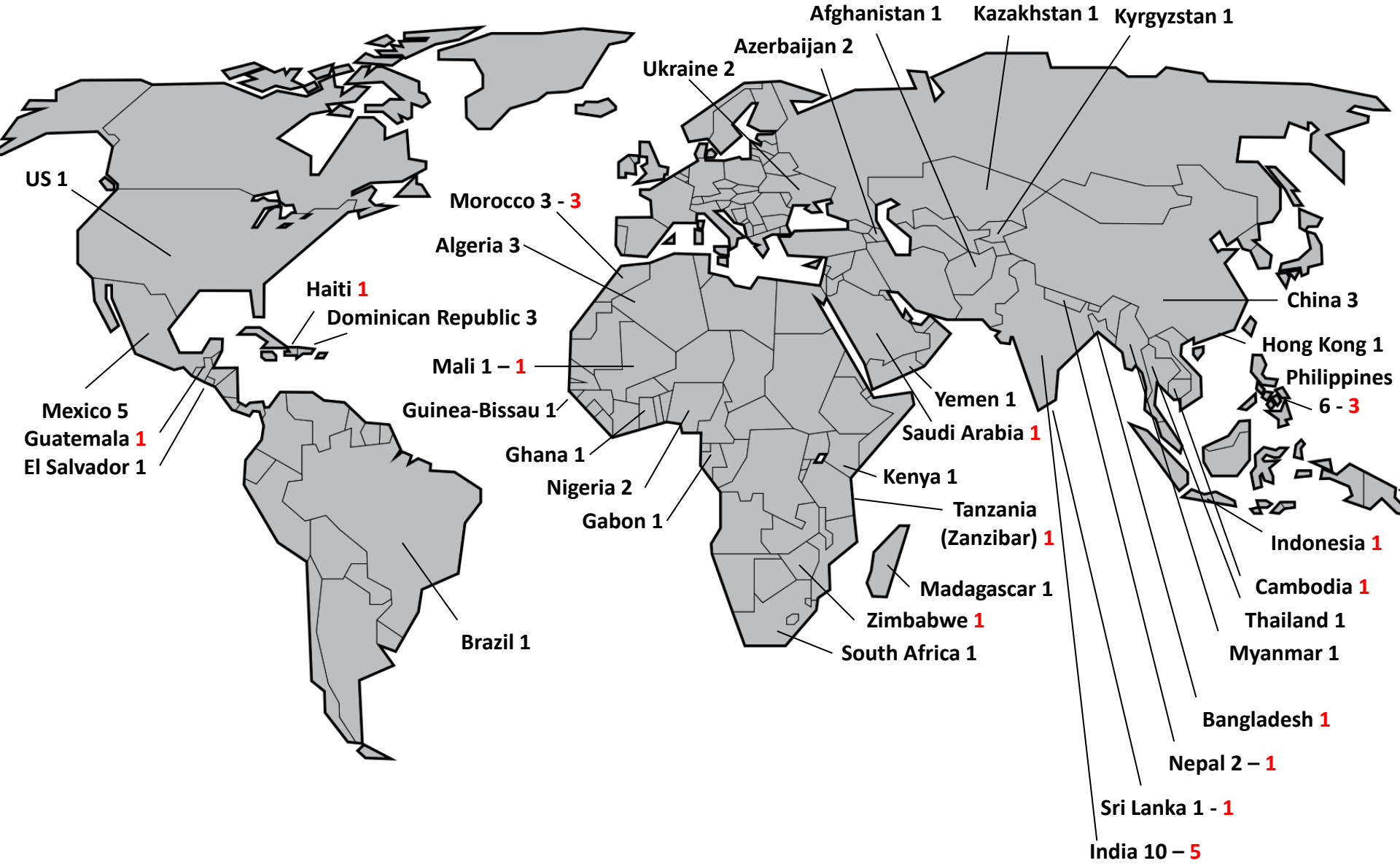
*and National Referral Unit for Tropical and Travel Medicine, Hospital Universitario La Paz-Carlos III, Madrid, Spain (unpublished data)

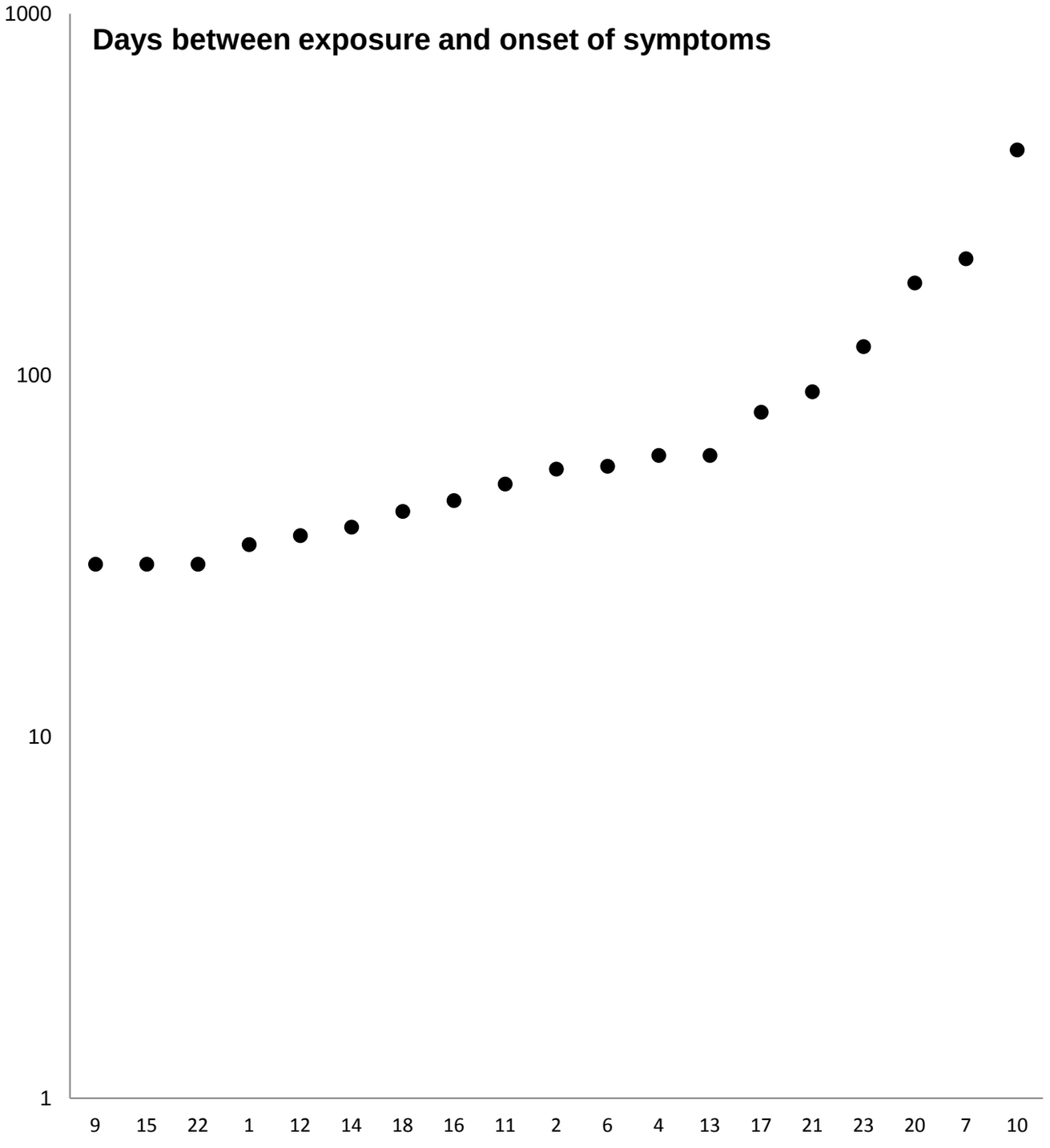
**Centre National de Référence de la Rage, Institut Pasteur, Paris, France (unpublished data)

***and GeoSentinel (unpublished data)

Table 2. Demographics, travel characteristics and source of exposure for 23 travel-associated rabies cases (2013-2019)

Category	**Subcategory**	**N (%)**
Age	≤ 5 years	1 (4)
	5-15 years	2 (9)
	16-59 years	16 (70)
	≥ 60 years	3 (13)
	Not documented (one middle aged individual)	1 (4)
Sex	Male	17 (74)
	Female	6 (26)
Place of residence	Europe	10 (44)
	Middle East	6 (26)
	US	3 (13)
	Asia	3 (13)
	Africa	1 (4)
Reason for travel	Migration to high-income country	8 (35)
	Visiting friends and relatives	6 (26)
	Tourism	6 (26)
	Business	2 (9)
	Expatriation to low income country	1 (4)
Source of infection	Dog	17 (74)
	Cat	2 (9)
	Raccoon-like animal, possibly *Ailurus fugens* (red panda)	1 (4)
	Unknown animal or not documented	3 (13)


Afghanistan 1
Kazakhstan 1
Kyrgyzstan 1
Azerbaijan 2
Ukraine 2
US 1
Morocco 3 - 3
Algeria 3
Haiti 1
Dominican Republic 3
China 3
Hong Kong 1
Philippines 6 - 3
Mali 1 – 1
Yemen 1
Mexico 5
Guinea-Bissau 1
Saudi Arabia 1
Guatemala 1
El Salvador 1
Ghana 1
Kenya 1
Nigeria 2
Tanzania (Zanzibar) 1
Gabon 1
Indonesia 1
Madagascar 1
Cambodia 1
Zimbabwe 1
Thailand 1
Brazil 1
South Africa 1
Myanmar 1
Bangladesh 1
Nepal 2 – 1
Sri Lanka 1 - 1
India 10 – 5


Days between exposure and onset of symptoms
1000
100
10
1
9
15
22
1
12
14
18
16
11
2
6
4
13
17
21
23
20
7
10