

Technical Appendix

for

Travel-Associated Rabies in Pets and Residual Rabies Risk, Western Europe

Florence Ribadeau-Dumas, Florence Cliquet, Philippe Gautret, Emmanuelle Robardet, Claude Le Pen, Hervé Bourhy

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Author affiliations:

Université Paris Dauphine, PSL Research University Paris, France (F. Ribadeau Dumas, C. Le Pen), Institut Pasteur, Paris, France (F. Ribadeau Dumas, H. Bourhy), French Agency for Food, Environmental and Occupational Health & Safety, Malzéville, France (F. Cliquet, E. Robardet), Assistance Publique Hôpitaux de Marseille, Marseille, France (P. Gautret), Aix Marseille University, Marseille, France (P. Gautret)

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1a: Rabies risk and its determinants in recent WE history

Canine rabies was eliminated from Western Europe (WE) in the early 20th century, mainly due to public health measures such as controlling stray dogs, enforcing the wearing of muzzles and slaughtering suspect animals [1]. In the 1940s, after viral adaptation from dogs to foxes in Poland, rabies spread to nearly all of Europe. After implementation of biannual aerial distribution of vaccine baits, 12 European countries eliminated terrestrial rabies [1,2]. Two years after the last case, those countries (re-)acquired from the World Health Organisation for Animal Health (OIE) a rabies-free status for non-flying mammals [3]. Nevertheless, WE still faces 3 types of rabies risk in animals.

The first, related to bat rabies, is not a major epidemiologic risk in Europe. Unlike in the Americas, rabies in European bats has never been linked to RABV, the lyssavirus species responsible for canine rabies and over 99% of human cases. European Bat Lyssaviruses and the other two recently-discovered viruses—Bokeloh-Bat Lyssavirus and Lleida virus—are ill-adapted to spill over to non-flying species. No transmission between non-flying mammals and only 3 confirmed human fatalities linked with these viruses have been reported since 1954 in Europe (only 1 in WE (UK)) [4]. The second risk corresponds to cross-border reinfections of vulpine rabies from rabies-enzootic European countries and has been observed in Italy in 2008 [5], in the Republic of Macedonia in 2010[6], in Greece in 2012[7] and in Slovakia in 2013[8], highlighting the need for constant rabies surveillance. The third risk, illegal importations or movements of infected animals from rabies-enzootic countries, may cause indigenous rabies cases or, more seriously, a rabies resurgence. Thus, Spain in 1975 lost its rabies-free status when illegal importation of a rabid dog from Morocco led to rabies in 81 pets and 1 human in a single year [9,10]. To avoid rabies introduction from infected areas, a European Pet Movement Policy (EUPMP) has been implemented through successive EU regulations laying down, in particular since 2003, the conditions for non-commercial movements of pet animals prior to EU entry. Almost every year, rabid pets are reported [11] in Europe due to border control failures, ignorance or active subversion of these rules.

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1b. Rabies situation in Western European countries until December 2013

Technical Appendix 1b. Rabies situation in Western European countries until December 2013

Country*	Date of last rabies case of indigenous origin in a human	Number of human cases 2001-2013[1]	Date of last indigenous rabies case in a non-flying mammal
Belgium	1922 [2]	0*	1999 [2,3]
France	1924	1 (2003: 1 case from a dog in Gabon)	1998 (in 2008, 2 dogs acquired rabies in France but these were secondary cases from a rabid dog importation)
Germany		6[4] (2004: 1 case from a dog or monkey in India 2004: 1 case from a dog in India, source of 3 cases in 2005 in 3 transplant patients[5] 2007: 1 case from a dog bite in Morocco[4])	2006 [6] (361 cases from 2000 to 2006)
Ireland	Before 1904 [2]	1 (2008: 1 case from an animal in South Africa)	1903 [2]
Italy	1968 [7]	1 (2011: 1 case from a dog in India [8])	2011 (No cases from 1992 to 2007) Rabies-free status from 1995 [9] lost in 2008 due to resurgence with 287 cases from 2008 to 2011
Luxembourg	Before 1966[2]	0	1998
Netherlands	1923	02 (2007: 1 case from a bat bite in Kenya 2013: 1 case from a dog bite in Haiti)	1988 [10]
Portugal	1960 [2]	1 (2011: 1 case from a dog in Guinea Bissau [11])	1960 [2]
Spain	1975 [2]	0	1978'[2]
Switzerland	1977 [12]	1 (2012: 1 US soldier with US bat rabies [13])	1996 [14]
United Kingdom	1902[15,16]	6 [17,18] (2001: 1 case from a dog in the Philippines 2001: 1 case from a dog in Nigeria 2002: 1 case from a bat (EBLV 2) in Scotland 2005: 1 case from a dog in India 2008: 1 case from a dog in South Africa 2012: 1 case from a dog in India)	1922 [15]

*Only those parts of the country situated in Continental Europe are considered in this table

†38 cases in Ceuta and Melilla (Spain) between 2000 and 2013 were not considered in this table because they are enclaves in North Africa, not the Spanish peninsula

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1c: Relevance of human post-exposure prophylaxis (PEP) to reduce WE rabies risk

Human rabies encephalitis—always fatal—can be prevented through PEP, including rabies vaccines sometimes prescribed with rabies immunoglobulins. As dogs and cats can be contagious up to 10 days before clinical signs, [1,2] the need for PEP must be evaluated even after exposure to asymptomatic pets. In most WE countries where rabies was recently eliminated (see **Technical Appendix 1b**), PEP recommendations are based on the WHO, which considers WE as a “low rabies-risk area” (mainly because European bat rabies is not differentiated from bat rabies in the Americas) [3–5]. Consequently, PEP is recommended for patients injured by local unobservable pets. The lack of specific “very low risk area” recommendations leads to discrepancies in practices and expenses not always based on epidemiologic reasoning [6]. For example, in the UK, the position of Public Health England (PHE) is based on WE OIE rabies-free status for terrestrial mammals. PHE considers that there is “no risk” of rabies following infection by WE dogs or cats, and consequently does not recommend PEP [7] (unless there is an alert in the area). PHE does not consider the history of OIE rabies-free status, whether long (e.g. the UK) or short (e.g. France, Belgium, Switzerland). However, because of sporadic cases of imported rabid animals, many WE countries, including France [8], Germany [9] and Switzerland [10], still recommend the WHO position and so PEP after exposure to an unobservable dog in their country. Residual risk in WE pets being defined as “no risk” (no PEP necessary) or “low risk” (PEP recommended after exposure to an unobservable pet) depending on stakeholders, it appears necessary to better rationalize and harmonize PEP recommendations in WE.

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2: Methods

Data and sources

Epidemiologic data on WE rabies cases among pets due to travel were first obtained from a literature review using PubMed (MEDLINE) from 2001 to April 2014 (cross-referencing “rabies” “importation” “travel” “dog” “cat” and “ferret”) and ProMED alert systems supplemented by peer-reviewed papers. Additional disease reporting systems were used, including the OIE World Animal Health Information Database (WAHID) interface (http://www.oie.int/wahis_2/public/wahid.php/Diseaseinformation/WI), the European Food Safety Agency’s annual report, and reports of the European Standing Committee on the Food Chain and Animal Health [1]. When lacking specific information on included cases, national records or rabies reference centers were consulted. Information was considered valid if not invalidated by any national or European rabies reference center and if found in at least 2 different reporting systems or published in peer-reviewed journals. Data collected concerned chronology, animal characteristics, rabies vaccination history, pet passport and health certificate, transportation mode, country of origin and destination, and number of PEP related to each case. Data on dog and cat populations per country were obtained from the European Pet Food Industry Federation [2].

Inclusion and exclusion criteria

We considered all rabid pets reported in WE, whether directly or indirectly linked to pet travel. The WE countries studied were Belgium, France, Germany, Ireland, Italy, the Netherlands, Portugal, Spain, Switzerland and the United Kingdom, restricted to continental Europe (Spain’s Ceuta and Melilla enclaves were excluded, for example, as was French Guiana). We did not consider countries with <1,000,000 inhabitants.

Bat and wildlife rabies cases were excluded (Germany before 2006 and Italy from 2008 to 2011 being concerned by wildlife rabies [3,4]).

Pet travel is herein defined as any non-commercial movement across an administrative border by a live cat, dog or ferret with its owner or authorized person. Thus, a rabid animal confirmed by WE reference laboratories but diagnosed in samples from animals that died outside WE [5] were not included. This concerned 2 dog cadavers imported for diagnosis: 1 from Afghanistan to France in 2009 and 1 from Nepal to Germany in 2001.

Rabies risk calculation

The number of contagious days over the study period was calculated for each country and for all WE according to review data. For each area (country or WE), the animals’ contagious period included period of contagiousness in the area before symptoms and from first symptoms to death. We defined then calculated P_A for each country and all WE according to a previous study in France [6]:

$$P_A = \frac{\sum \text{number of contagious days for pets in the area between 2001 and 2013}}{\text{number of pets in the area} * \text{number of days between 2001 and 2013}}$$

Key assumptions

It was assumed that the number of cats and dogs (based on data from 2010 [2]) was stable over the study period (2001-2013). Dogs and cats were considered to be contagious 10 days before initial symptoms [7–9].

Analyses

Correlation tests were performed to assess the relationship between different parameters (dog population, density of dogs, dogs per inhabitant, number of tourists visiting Morocco) and P_A or number of contagious days. Considering un-normality and the limited size of the dataset (10 countries), a non-parametric Spearman-Rank Correlation test was used. Analyses were undertaken using Excel2013© (Microsoft.Inc) and R 3.0.1 (R Development Core Team, 2006).

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3: Factors for which correlation with P_A has been studied

Technical Appendix 3: Factors for which correlation with P_A has been studied

Country	Population size			Area* (km ²)	Dog/capita	Cat/capital	Dog/km ²	Cat/km ²	Number of tourists to Morocco in 2011
	Human [1] 1 .1. 2011	Dogs [2] 2010	Cats [2] 2010						
Switzerland	8,037,000	445,000	1,507,000	41,290	0.06	0.19	11	36	<200,000
France	64,994,000	7,595,000	10,965,000	547,030	0.12	0.17	14	20	1,776,000
Belgium	11,000,000	1,331,000	1,884,000	30,528	0.12	0.17	44	62	258,000
Germany	81,751,000	5,300,000	8,200,000	357,021	0.06	0.10	15	23	219,000
Spain	46,152,000	4,720,000	3,385,000	505,580	0.10	0.07	9	7	693,000
Netherlands	16,655,000	1,493,000	2,877,000	41,526	0.09	0.17	36	69	<200,000
United Kingdom	62,515,000	8,000,000	8,000,000	244,820	0.13	0.13	33	33	352,000
Ireland	4,570,000	425,000	310,000	70,280	0.09	0.07	6	4	<200,000
Italy	60,626,000	7,000,000	7,400,000	301,230	0.12	0.12	23	25	211,000
Portugal	10,572,000	1,940,000	991,000	92,042	0.18	0.09	21	11	<200,000
All WE	366,872,000	38,249,000	45,519,000	2,231,347	0.10	0.12	17	20	-
Mean	36,687,200	3,824,900	4,551,900	223,135	-	-	-	-	-

P_A : Calculated risk that a given pet (dog or cat) is rabid on a given day in a Western European country in relation to pet travel

WE= Western Europe

*http://fr.wikipedia.org/wiki/Liste_des_pays_d%27Europe_par_superficie

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http://www.google.fr/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=0CCkQFjAB&url=http%3A%2F%2Fwww.fediaf.org%2Ffileadmin%2Fuser_upload%2Ffacts_and_figures_2010.pdf&ei=DYRxVdG-IIHIUaLOgcAF&usg=AFQjCNFzcqh4D_o_cJ1XbUaXimxFeIDclw&sig2=XM30honrgIT2uxDAk3uvJA&bvm=bv.95039771,d.ZGU (accessed June 5, 2015).

Year	Country of	Date of	Date of entry in	Date of	Date of	Species	Age	Conditions	Circumstances	Vaccination*	Pet passport	Health	Travel mode	Count
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4a: Animal rabies cases in Western European countries related to a trip to or importation from an endemic country, 2001-2013.

	declaration	ownership	final country	first symptoms	animal death			of ownership in the endemic country	of dog diagnosis	*		Certificate		rabies infect
2001	France	03/26/2001	03/31/2001	5/19/2001	5/21/2001	dog	puppy 3 mo	Adoption	Sick	No	?	No	Road	Moro
2002	Germany	November (before the 10th) 2001	12/21/2001	12/23/2001	01/9/2002	dog	puppy 1 mo	Adoption	Sick	Yes	No	Yes	Plane	Azerb
2002	France	?	08/16/2002	08/29/2002	09/2/2002	dog	puppy 2.5 mo	Gift	Sick	No	?	Yes	Road	Moro
2003	Switzerland	06/25/2003	05,?,/2003	007/15/2003	07/19/2003	dog*	puppy 2 mo	Adoption from a shelter*	Sick	?	?	?	?	Moro
2004	Germany	before January 2004	01/6/2004	02/2/2004	02/7/2004	dog	puppy 8 mo	?	Customs control (quarantine)	No	No	No	Plane	Moro
2004	France (Through Melilla and Spain)	NA	01/?/2004	01/23/2004	01/26/2004	dog†	adult 4y	NA French dog	Sick	Yes	No	No	Road	Moro
2004	France (Through Ceuta and Spain)	?	07/11/2004	08/17/2004	08/21/2004	dog	puppy 4 mo	Adoption	Bite	No	?	No	Road	Moro
2004	France (Through Spain)	05/9/2012	05/11/2004	05/10/2004	05/15/2004	dog	puppy 6 mo	Gift	Sick	No	?	?	Road	Moro
2007	France (Through Portugal and Spain)	NA	10/20/2007 in Spain then 2-3 days in Portugal then 10/23/2007 in Spain then 10/28/2007 in	11/2/2007	11/12/2007	dog†	adult	NA French dog	Sick	Yes	No	No	Road	Moro

France														
2007	Belgium	07/?/2007	07/7/2007	10/16/2007	10/20/2007	dog	puppy 1 mo	Adoption	Sick	No	No	Yes	Plane	Morocco
2008	France	NA	NA	01/2/2008	01/5/2008	dog†	adult	NA French dog	Retrospective (secondary cases)	No	?	?	NA	France
2008	France	NA	NA	02/15/2008	02/19/2008	dog†	puppy 9 mo	NA French dog	Retrospective (secondary cases)	No	?	?	NA	France
2008	France (Through Belgium)	01/4/2008	04/07/2008 in Belgium 04/13/2008 in France	04/16/2008	04/21/2008	dog	puppy 4 mo	Adoption found	Sick	Yes	No (microchip)	Yes	Plane then Road from Belgium to France	Gambia
2008	United Kingdom	04/12/2008	04/17/2008	04/23/2008	04/25/2008	dog	puppy 2.5 mo	Adoption found	Customs control (quarantine)	Yes	No	?	Plane	Sri Lanka
2008	France (Through Spain)	10/12/2008	10/12/2008	10/30/2008	11/10/2008	dog	puppy 3 mo	Adoption found	Sick	No	?	No	Road	Morocco
2008	Germany	07/15/2008	07/15/2008	12/27/2008	12/29/2008	dog	puppy 1.5 mo	Bought	Sick	No	No	?	Road	Croatia
2010	Germany	02/27/2010	02/27/2010	3/18/2010	03/21/2010	dog	puppy 2 mo	Bought	Sick	No	Yes	Yes	Road	Bosnia Herzegovina
2011	France	07/11/2011	08/1/2011	08/5/2011	08/7/2011	dog	puppy 3 mo	Adoption found	Sick	No	No	No	Road	Morocco
2012	Netherlands (Through Spain)	1/28/2012	02/04/2012 in Spain 02/11/2012 in the Netherlands	2/12/2012	2/15/2012	dog	puppy 2 mo	Bought	Bite	No	Morocco: No (microchip) Spain: Yes	Yes	Road to Spain then Plane to Netherlands	Morocco

2013	Spain [#]	NA	04/13/2013	05/27/2013	6/1/2013	dog [†]	adult 4y	NA Spanish dog	Bite	Yes	Yes (microchip)	?	Road	Moro
2013	France	10/25/2013	10/13/2013	10/25/2013	10/28/13	cat	kitten 2 mo	Adoption found	Sick	No	No	Yes	Plane	Moro

NA = Not Applicable

? = Data unavailable

WE= West Europe

mo= month

*Animal from an endemic country bought or adopted from a shelter

†Animal raised in the Western European country where rabies was diagnosed

‡For the calculation of the number of contagious days: day of entry in the country and day of death are included, but day of departure from the country is not

§The owners lived in a van

¶Approximation based on incomplete available data

#2 months before the dog's owners had tried to cross the border legally, but were denied entry because the seroneutralisation assay according to EU regulation had not been done before the trip to Morocco

** Animals are considered as vaccinated whether the rabies vaccination is up-to-date or not (this information is unavailable most of the time)

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Technical Appendix 4b: Country of diagnosis and transit of pets diagnosed rabid in a Western European country. 2001-2013

Country (n=21)	Number of rabid pets with the following country of diagnosis n (%)	Number of rabid pets with the following WE country of transit between infection and diagnosis n _t	Total of pets with transit or diagnosis in the country n _{td} = n + n _t	Mean number of rabid pets linked with travel in 100 years m [‡]
Belgium	1 (5%)	1	2	15
France	10+2 secondary cases (57%)	0	12	92
Germany	4 (19%)	0	4	31
Ireland	0 (0%)	0	0	-
Italy	0 (0%)	0	0	-
Netherlands	1 (5%)	0	1	8
Portugal	0 (0%)	1*	1	8
Spain	1 (5%)	6†	7	54
Switzerland	1 (5%)	0	1	8
United Kingdom	1 (5%)	0	1	8
WE	21 (100%)	7 pets with a transit country (of which 1 has 2 transit countries)	21 pets (of which 8 transits where reported)	162 pets (of which 62 transits would be reported)

*E= Western Europe

†A dog from Morocco diagnosed rabid in France in 2007 transited through Portugal and Spain. The period of contagiousness started in Spain after transit through Portugal so it is reported in this table but no days with a rabid dog were taken into account in Portugal for this event.

‡For some dogs from Morocco that arrived in France via Spain, no days of attendance in Spain are reported. Those cases are reported in this table. ‡m = n_{td} × 100 / 13, m is calculated under the assumption that, during the 100-year period, the mean annual number of rabid pets linked with travel is the same as that observed between 2001 and 2013.

4b: Country of diagnosis and transit of pets diagnosed rabid in a Western European country. 2001-2013

4c: Complementary results

Fifteen dogs (all puppies under 6 months) and 1 kitten originated from endemic countries outside WE: 12 (75%) were found or gifted in the endemic country, 3 were bought abroad and 1 was adopted from a shelter (in Switzerland where it had been illegally imported). Five dogs raised in WE (4 adults, 1 puppy) acquired rabies outside WE, including 3 in Morocco.

Without contamination dates, it was impossible to calculate the average incubation period, but it was over 33 days as the average period between an animal entering WE and first symptoms was 33 days [IC95: 10-56]. The average contagious period was 16 days, starting 2 days before entering WE, and including 14 days in WE (8 asymptomatic and 6 symptomatic). For 1 dog, symptoms began before entering WE.

5: Evolution of the number of imported rabid pets and their secondary cases

Only 1/19, i.e. 5%, of 2001-2013 imported rabid pets led to secondary cases (2 cases in dogs) compared to 4/17, i.e. 24%, in the 1968-1995 period (with 1 to 7 secondary cases per alert) and to the Spanish situation in 1975, when a rabid Moroccan dog infected 81 pets and 1 human [1,2].

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6: Study limitations and robustness

We did not consider whether the contagious period occurred during quarantine (as in the 2008 UK case), during veterinary observation or outside those contexts. Risk management is easier during quarantine and veterinarian observation. First, because—unlike the general population—veterinarians and quarantine workers should be vaccinated prior to exposure [1], and second, because risky contacts are limited and more easily and quickly handled. Thus the UK rabies risk is probably over-estimated in our study (1 rabid pet imported in 13 years, compared to 1 in 170 following a DEFRA assessment [2] (DEFRA assumed 90% compliance with EUPMP and did not consider a rabid pet in quarantine as entering the UK). We considered, based on the WHO post-exposure animal observation period, that the asymptomatic contagious period was 10 days rather than 14 (Spain's observation period) or 15 (UK and France's period). However, had we considered a 15-day period for the 14/20 dogs which started their contagious period in WE, we would have had 238 instead of 168 asymptomatic contagious dog days in WE. Thus P_A would have increased to 1.96×10^{-9} which is still very low. Our review could suffer from missing information regarding imported animal cases. However, our results are probably near-exhaustive since rabies notification is mandatory in WE, and the quality of health watch and reporting networks is satisfactory. From 2001 to 2013, no human fatalities were observed after contact with 1 of the 21 rabid pets. Therefore, the average individual risk of rabies linked with pet travel is $< 2.10 \times 10^{-10}$ /year, which is notably less than the 8.2×10^{-6} /year individual risk of rabies in the world and very low even regarding other risks considered very low, such as death from dog bites (7.1×10^{-8}), road accidents (8.3×10^{-6}) or lightning (5.2×10^{-8}) [2,3].

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7: Political implications

Finally, EU and WE countries should:

- Improve information to travelers to or from rabies-enzootic countries (especially North Africa) about the risk of rabies if exposed abroad or traveling with pets. For example, information about rabies risks could be made available on transport from rabies-enzootic countries to WE (on tickets, in the line for customs or boarding or on posters in ferries and airports).
- Enhance information to professionals (especially veterinary and customs services) involved in the application of EUMP as initiated recently with training courses organized by the European Commission (<http://www.foodinfo-europe.com/training-programs/mdc-presentation>).
- Check in each country, but especially in areas with non-rabies-free borders (such as Ceuta and Melilla) and ports, airports and land border crossings with heavy traffic to/from enzootic countries, that sufficient human resources and equipment are available for reliable border controls of all pets.
- Help the main countries involved in rabies importation to improve and successfully control indigenous canine rabies, possibly through partnerships. The EU could, for example, promote mass dog vaccination campaigns in those countries as it has already promoted mass oral vaccination campaigns for wildlife in neighboring Eastern and Southern European countries with fox rabies. Those countries' residents and European travelers would no longer be exposed to rabies, WE patients would be saved from unnecessary and possibly harmful PEP and the WE public health system would avoid costly alert management.