Update on human rabies in a dog- and fox-rabies-free country.

J.P. Stahl, P. Gautret, Florence Ribadeau-Dumas, C. Strady, G. Le Moal, F. Souala, J. Maslin, B Fremont, Hervé Bourhy

Disponible en ligne sur
ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com
Médecine et maladies infectieuses 44 (2014) 292–301

Médecine et maladies infectieuses

General review

Update on human rabies in a dog- and fox-rabies-free country

La rage humaine dans un pays reconnu indemne de rage canine et de rage vulpine : état des lieux

J.-P. Stahl[a,*], P. Gautret[b], F. Ribadeau-Dumas[c], C. Strady[d], G. Le Moal[e], F. Souala[f], J. Maslin[g], B. Fremont[h], H. Bourhy[c]

[a] *Maladies infectieuses et centre antirabique, CHU, BP 217, 38043 Grenoble, France*
[b] *Centre antirabique, CHU Nord, 13915 Marseille, France*
[c] *Centre national de référence sur la rage, Institut Pasteur, 75015 Paris, France*
[d] *Groupe Courlancy, cabinet d'infectiologie, clinique Saint-André, 51100 Reims, France*
[e] *Service des maladies infectieuses et centre antirabique, hôpital la Milétrie, 86021 Poitiers, France*
[f] *Centre antirabique, CHU Ponchaillou, 35033 Rennes, France*
[g] *SLB JsBio, laboratoire espace santé du Golfe de Saint-Tropez, 83580 Gassin, France*
[h] *Service des admissions et des urgences, centre antirabique, centre hospitalier, 55107 Verdun, France*

Received 15 April 2014; received in revised form 29 April 2014; accepted 22 May 2014
Available online 8 July 2014

Abstract

Rabies is responsible for 50,000 deaths per year worldwide. Mainland France has been officially freed from rabies in non-flying animals since 2001.

Method. – We wanted to provide an update on the French situation, using published data, and describe possible options since official guidelines are lacking.

Results. – Post-exposure prophylaxis (PEP) (early and careful cleaning and dressing of the wound, vaccination, and in case of high-risk exposure, injection of specific anti-rabies immunoglobulins) is known to be efficient except in rare cases. It is recommended after grade II contact (+specific immunoglobulins in immunodepressed patients), or grade III contact (vaccination + immunoglobulins).

Discussion. – Mainland France being rabies-free, 3 options may be considered in case of bite by a dog or a cat that cannot be monitored in France: (a) consider the risk of rabies as null, so no PEP should be administrated, whatever the severity of bites; (b) consider there is a weak but lethal risk, so the international recommendations should be applied, using immunoglobulins in some cases; (c) consider that the risk is extremely low but cannot be excluded, and that the patient should be vaccinated to be protected, but without adding immunoglobulins (whether in case of grade II or III bites).

Conclusion. – There are no national guidelines for rabies in France, and so the physician managing the patient is the one who will decide to treat or not.

Keywords: Rabies; Post-exposure prophylaxis; Anti-rabies immunoglobulins

Résumé

La rage entraîne 50 000 décès annuels dans le monde. La France métropolitaine a été déclarée indemne de rage des animaux non volants en 2001.

Méthode. – Nous avons fait le point sur la situation française, en utilisant les données de la littérature, et exposé les options possibles en l'absence de recommandations officielles.

Résultats. – La prophylaxie-post-exposition (PPE) (nettoyage précoce et minutieux de la plaie, administration d'un vaccin et, en cas d'exposition particulièrement à risque, l'injection d'immunoglobulines antirabiques) est réputée constamment efficace, à de rares exceptions près, et recommandée après un contact de catégorie II (+immunoglobulines antirabiques chez les immunodéprimés) ou III (vaccination + immunoglobulines).

* Corresponding author.
E-mail address: jpstahl@chu-grenoble.fr (J.-P. Stahl).

http://dx.doi.org/10.1016/j.medmal.2014.05.002

Discussion. – Compte tenu du statut indemne de rage terrestre de la France métropolitaine, 3 attitudes seraient possibles en cas de morsure par un chien ou chat impossible à surveiller, en métropole : (a) considérer le risque rabique comme nul donc n'administrer aucune PPE quel que soit le degré des morsures ; (b) considérer qu'un risque minime mais gravissime subsiste, et donc qu'il faut appliquer les recommandations internationales, impliquant parfois l'utilisation d'immunoglobulines ; (c) considérer qu'un risque ne peut pas être totalement exclu mais qu'il est faible et que, pour conférer une protection au patient, il faut le vacciner contre la rage, sans ajouter d'immunoglobulines (que sa morsure soit de catégorie II ou même III).

Conclusion. – En l'absence de recommandations officielles nationales en France, la décision reste dans les mains du praticien qui a en charge la personne mordue.

Mots clés : Rage ; Prophylaxie post exposition ; Immunoglobulines antirabiques

1. Introduction

Rabies is a lethal zoonosis caused by lyssaviruses, neurotropic viruses transmitted from animal to humans by bite, scratch, or licking on wound or on mucosa. Inter-human transmission has been reported incidentally, following transplant of infected tissue or organs. The incubation period of the disease is usually 20 to 60 days in humans; but it can sometimes range from several days to several years in rare cases. The disease leads to death without treatment but this may be prevented by an adequate post-exposure prophylaxis (PEP) applied before the onset of rabies clinical symptoms [1,2]. Access to PEP, vaccines, and good quality immunoglobulins, is still difficult or impossible for economic, social, and healthcare policy reasons in many countries [3].

As a result rabies still causes around 50,000 deaths every year worldwide [4]. Asia is the most affected continent, especially India where 20,000 deaths are reported per year [1]. The incidence is also high in Africa, with an estimated 40% of cases.

2. The various lyssaviruses, their reservoirs and worldwide geographic distribution

Twelve species of lyssavirus have been identified so far, and most of them are carried by various bat species (Table 1). Each lyssavirus is closely adapted to a preferential host acting as vector and reservoir. As all RNA viruses, the lyssaviruses present a high rate of incorporation errors during replication of their genetic material, conferring them a high mutation speed and a rapid adaptability to new environmental conditions, and thus sometimes to new animal species [5,6]. Finally, many human interventions (translocation of infected animals, anti-rabies vaccination of domestic animals and wild fauna, evolution of human behavior, etc.) have constantly modified the genetic nature of circulating viruses and the epidemiology. All of these factors participate in the epidemiological variations observed in a given geographic region.

New lyssaviruses have been periodically identified, especially in bats. This is the case of the Bokeloh bat lyssavirus isolated in Natterer's bats in Germany in 2010 and in France in 2012 and 2013. The pathogenic power of most of these viruses for humans remains unknown, even though one of these (Irkut virus) is suspected to have caused a human case of rabies in Russia in 2007 [7]. It is thus crucial to closely monitor of rabies on the national level, but also at the European and international level so as to quickly identify the emergence or the re-emergence of risks.

Rabies has a very wide geographic distribution worldwide, with various risk levels depending on the area considered [8]. Animals may also be infected with various lyssaviruses depending on the regions. The main reservoir animals (sensitive species that maintain the epidemiological cycle) are carnivores (dogs, red foxes, raccoon dogs, raccoons, mongoose, arctic foxes) and bats. These animals mainly infected humans directly.

Many other mammals (for example monkeys, camels, rodents, etc.) may sometimes be infected and become vector or intermediate host (species which do not maintain the epidemiological cycle). Nevertheless, these transmission features remain much less frequent than transmission to humans by carnivores, and worldwide, more than 99% of human rabies cases are due to a dog bite [4]. The geographic distribution of reservoir species according to viral species is described in Table 1 [9,10].

3. Recent evolution in Europe

The national oral vaccination programs for wildlife, which were initiated in Europe in 1978, resulted in elimination of rabies in Western and Central European countries. Rabies is still present in Baltic countries and in neighbor EU countries [11]. A new development is always possible, as demonstrated by the reintroduction of vulpine rabies in Venetia from Slovenia and Croatia in 2008 [12], or in Greece in 2012 [13].

Two different epidemiological presentations have been observed in humans, in Europe: there are still autochthonous rabies cases in Eastern European countries and importation cases mainly in Western Europe in travellers infected during their trip in enzootic zones [14].

4. Rabies in France

The last case of autochthonous rabies in continental France was reported in 1924. Twenty-one cases have been diagnosed

Table 1
Classified species of lyssaviruses, reservoirs and worldwide distribution.
Espèces reconnues de lyssavirus, principaux réservoirs et répartition.

Viral species	Usual reservoir	Distribution
Rabies virus	According to regions: dog, wild carnivores (red fox, polar fox, raccoon dog, jackal, mongoose, big-eared fox, skunk, raccoon) Insectivorous bats (and blood-feeding bats on both American continents exclusively)	Asia, Africa, America, Europe
Lagos bat virus	Frugivorous bat, cat, dog	Africa
Mokola virus	Shrewmouse, cat, dog, rodent	Africa
Duvenhage virus	Insectivorous bats	Africa
European bat Lyssavirus1	Insectivorous bats (most frequently the common big brown bat), cat, sheep, beach marten	Europe
European bat Lyssavirus 2	Insectivorous bats (most frequently *Myotis* sp.)	Europe
Australian bat Lyssavirus	Insectivorous and frugivorous eating bats (*Pteropus* sp., "flying fox")	Australia
Aravan virus	Insectivorous bats, discovered in 1991 in a lesser mouse-eared bat (*Myotis blythi*)	Central Asia
Irkut virus	Insectivorous bats, discovered in a greater tube-nosed bat (*Murina leucogaster*)	Asia
Khujand virus	Insectivorous bats, discovered in 2001 in a whiskered bat (*Myotis mystacinus*)	Central Asia
West Caucasian bat lyssavirus	Insectivorous bats, discovered in Schreiber's long-fingered bat (*Miniopterus schreibersii*)	Central Asia
Shimoni bat virus	Insectivorous bats, discovered in 2009 in Commerson's leaf-nosed bat (*Hipposideros commersoni*)	Africa

in France since 1970, all related to an animal exposure having occurred outside of continental France except for 1 case due to a corneal graft from an Egyptian donor [15]. The 3 last cases of human rabies in France were observed in 2004, 2008, and 2014. The first one was a child licked on facial mucosa by a dog during a stay in Gabon who died in France [16], the second was an adult diagnosed in French Guiana, contaminated by a bat rabies virus (desmodine type) carried by bats in French Guiana, the contamination origin of which was not discovered [17–19]. The most recent case occurred in an adult returning from a 6-month stay in Mali, and the exact circumstances of his contamination could not be determined.

Mainland France is currently officially rabies-free in non-flying mammals according to the World Organization for Animal Health (OIE) criteria. The last case of vulpine rabies was observed in 1998, and France became rabies-free in non-flying mammals in 2001. Some cases of rabies related to importation have been incidentally reported since 1968. Nine cases were reported in dogs between 2001 and 2011 (1 in 2001, 1 in 2002, 3 in 2004, 1 in 2007, 3 in 2008, and 1 in 2011) and 1 case in a cat in 2013. All these cases were related to an illegal importation of dogs and a cat from countries where canine rabies was endemic (Morocco and Gambia for the recent cases) during their incubation period, except for 2 cases in early 2008 in dogs having never left France. The investigations proved that these 2 cases, even though considered as autochthonous according to the OIE code, were indirectly related to an imported rabies case from Morocco, in late 2007 [20]. France lost its rabies-free status in February 2008, following these 2 cases of secondary and tertiary transmission on the national territory, according to the OIE definition; the rabies-free status was recovered only in February 2010. The loss of this status for 2 years did not change the national sanitary management measures, or the rules for exchanges or exportations.

Currently, the only infected autochthonous animals in mainland France are bats (58 positive cases from 1989 to December 2011). Rabies due to the European bat Lyssavirus (EBLV-1) was diagnosed in a cat in Vendée in 2007, but secondary transmissions following this type of contamination has never been reported [21]. The bat lyssavirus in mainland France, the European Bat Lyssavirus 1a, 1b, and 2, and the Bokeloh bat lyssavirus (Table 1) are different from the rabies virus responsible for rabies in foxes and dogs, and for most confirmed human cases; but they can potentially be transmitted to humans. Three laboratory-confirmed human cases have been recorded in Europe since 1977, but none in France [21].

The main virus reservoirs in French Guiana are bats and especially blood-feeding bats ("vampire bat", *Desmodus rotundus*). Thirteen cases of animal rabies were identified in French Guiana from 1989 to 2008: 10 in bovines, 2 in dogs, and 1 in a cat, all infected by the vampire bat virus (genotype 1). A case of rabies was diagnosed in a frugivorous bat in which a desmodine rabies virus was isolated in October 2009. It was the first time that a rabies virus had been isolated in a bat in French Guiana (NRC data). French Guiana is currently canine rabies-free and thus remains officially rabies-free in non-flying mammals (according to the OIE definition) [22]. The vaccination of domestic carnivores, bovines, equines, sheep and goats nevertheless remains mandatory because of the proximity with Brazil and Surinam, but it cannot be performed every year for all the herds.

5. Dog bites

There is no systematic recording of humans having been bitten by animals in France.

The authors of some studies conducted in France and abroad (Europe and North-America) mentioned that dog bites led a lot of patients to the emergency unit every year [23–29] and caused many hospitalizations [23,27], with an increased incidence in summer [27,30]. The wounds are more frequent in the youngest children, more severe [31], and often located on the head and neck [23,32] that may leave physical, esthetic, and psychological sequels [33]. Most of the time, the person who was bitten knew the dog and the attack occurred at home [26,31].

6. The current recommendations

Rabies causes encephalitis with very different symptoms depending on the individual and on the species considered; there is no curative treatment for rabies after the onset of symptoms and it is always lethal. The early biological diagnosis of the infection (before the onset of symptoms) is not possible in humans.

Preventing the disease is thus crucial, and relies on the administration of PEP that is always effective, except for rare cases. Close to 15 million of PEP are administrated every year worldwide. The WHO estimates that PEP helps avoid 330,304 deaths per year in Asia and in Africa [1].

The prevention of human rabies, following exposure to an animal presumed infected, is based on an early and careful cleaning of the wound, on administration of a vaccine produced on cell culture and, in case of high-risk exposure, injection of rabies immunoglobulins (RIG).

The question raised for any bite or scratch is thus the appropriate indication of PEP, with or without immunoglobulins.

To these measures of medical prophylaxis in humans are added some measures of rabies prophylaxis in animals, monitoring of suspected animals, and prevention of infection in animal reservoirs (especially pet dogs), and finally global measures of information for potentially exposed populations and healthcare professionals.

6.1. According to the WHO [1]

The indications for post-exposure vaccination, associated or not to the administration of RIG, depend on the type of contact with the suspected rabid animal. The types of contacts are as follows:

- grade I: touching or feeding animals, licks on intact skin;
- grade II: nibbling of uncovered skin, minor scratches or abrasions without bleeding, licks on slightly abraded skin;
- grade III: single or multiple transdermal bites or scratches (with bleeding), licks on broken skin; contamination of mucous membrane with saliva from licks, contacts (superficial or deep bites or scratches, contact with a wound or mucous membrane) with bats.

No prophylaxis is necessary after a grade I contact, whereas immediate vaccination and local treatment of the wound is recommended after a grade II contact (+ RIG for immunocompromized patients), and immediate vaccination associated to the administration of RIG and local treatment of the wound, after a grade III contact for patients not previously vaccinated.

Table 2
Effectiveness of immunoglobulins used for post-exposure treatment [36,37].
Efficacité des immunoglobulines antirabiques en post-exposition [36,37].

Passive anti-rabies immunotherapy	Number of patients treated after being bitten by a rabid animal	Number of deaths
Yes	3,150	17[a]
No	147	36

[a] Ten delayed PEP administrations (5–30 days after the bite), including some stitched wounds.

All the bites and scratches must be carefully cleaned and washed, immediately or as soon as possible (for 15 minutes), with running water and soap/detergent, then with an antiseptic.

PEP may be stopped if an appropriate laboratory examination proved that suspected animal did not carry rabies or, in case of a dog, a cat, or a pet ferret, if the animal is still asymptomatic after a 15-day observation period according to regulations in France. The treatment may be delayed until obtaining the result of surveillance of the animal, in zones at low risk for rabies, in case of bites from apparently healthy dogs and cats, not known to have travelled. The causative animal's vaccinal status should not be considered as a reason to rule out prophylaxis even if this considerably reduces risks [34].

The WHO recommendations were proposed for countries in enzootic areas. Applying these strictly in rabies-free countries would lead to administrating many useless PEP.

The WHO Europe mentioned that a risk assessment should be performed by a medical expert competent in local rabies epidemiology. The healthcare authorities may not recommend PEP according to performances of the epidemiological surveillance relying on laboratories [35].

Passive immunotherapy associated to vaccination for face bites was proved useful in Iran and in the USSR in the second half of the 20th century. The results of a series of studies coordinated by the WHO allowed determining the protocol [36]. But neither randomized controlled trial nor cohort study including non-treated groups of humans can be ethically allowed. Thus the effectiveness data of the RIG scheme comes from field experience on individuals exposed to laboratory-confirmed canine rabies. Today its effectiveness is estimated at more than 99%. On the other hand, it is much more difficult to determine what would be the effectiveness of the vaccine alone. Only 10% of exposed individuals receive RIG according to WHO estimations, whereas more than 50% of these were exposed to a grade III contact [37]. Many countries in Africa are frequently out of RIG or do not use it, lacking adequate financial means [2]. Likewise in Asia, immunoglobulins are administrated to 22% of patients receiving PEP whereas 43% of these were exposed to a grade III contact [38]. Most recorded cases of human rabies in these countries concern individuals not having received any PEP, having begun PEP late, or not having completed the vaccination schedule [39–42]. The added value of RIG administration would be crucial in case of severe bites, especially in richly innervated areas such as the head, neck, and hands, and in case of multiple bites (cf. Table 2). It would be less important in other case. Nevertheless, no scientific data currently supports these assertions.

Most current RIG products, especially immunoglobulins of human origin and fragments $F(ab')_2$ of equine origin, are very effective and cause minimal adverse reactions [36].

In France, an animal having bitten is monitored mandatorily for a little longer than recommended by the WHO (15 of 10 days), when possible. The objective is to restrict therapeutic indications to victims of a bite by an animal strongly suspected to be or confirmed infected. There are no specific recommendations for the indications and the PEP scheme in France.

7. Analysis of practices in France; possible malpractice, problems encountered

The number of patients consulting an anti-rabies medical centre, and the number of PEP delivered from 2003 to 2009 slightly decreased according to NRC rabies data, but the ratio consulting patients/treated patients remained stable.

Contact with an animal suspected to be rabid occurred abroad in 9.2% of cases, in 2011. The number of consultations following risk of exposure to rabies abroad has been constantly increasing: from 200 in 1982 to 746 in 2009 [43].

No case of autochthonous human rabies was reported in continental France from 2001 to 2011, while 84,000 individuals consulted in an anti-rabies medical centre after exposure in continental France, including around 1500 for exposure to bats. This was due to:

- the very low risk of virus circulation in a country rabies-free in non-flying mammals;
- the effectiveness of patient management by the network of anti-rabies medical centres;
- the effectiveness of the laboratory diagnosis performed by the rabies NRC allowing a rapid initiation of anti-rabies prophylaxis when it is justified, or conversely to stop PEP if results are negative;
- the capacity of sanitary veterinarians to detect rabid animals, imported illegally or legally;
- the speed with which concerned services can prevent or stop a possible chain of transmission, in case of illegal importation;
- the non-systematic transmission of the virus in case of a bite.

Keeping a low risk level requires competent personnel, in animal and in human healthcare, to perform all these actions in every region, as well as easy access to reliable sources of information, with updated local and international epidemiology and mode of prophylaxis use (treatment protocols, etc.).

The situation in France is paradoxical. There is no marked decrease in the number of number of PEP despite the eradication of canine rabies. This may be due to the absence of any specific recommendations for France, especially since the country has been considered as rabies-free in non-flying mammals. The WHO considers that France presents a weak risk of rabies (because of bat of rabies) like the USA (where the situation is relatively controlled but where cases of selvatic rabies are still observed).

The Health Public agency (UK) considers that France having been declared rabies-free in 2001, the risk consecutive to a bite in France by a non-flying mammal is null. The recommendation in Great Britain is thus to use neither vaccine nor anti-rabies immunoglobulins even after having been bitten by a wandering dog in France. Nevertheless, during an alert as in the city of Argenteuil after identifying a rabid kitten coming from Morocco at the end of 2013, the same agency considered the risk as not null in a city where the alert has been issued, and only in that place [44].

Furthermore, PEP is still used after exposure to animal species the role of which in rabies epidemiology is doubtful. There is a tendency to use less PEP after contact with a dog (which nevertheless remains the most frequent contact) was observed, when considering the 6 main species related to exposure in individuals consulting in an anti-rabies medical centre from 2006 to 2009. Conversely, there was a trend to more PEP after contact with cats, whereas no autochthonous case or case due to illegal importation, related to a common rabies virus (RABV species), had been observed in these animals until 2013 in France. The rate of exposure to bats more than doubled during that period and that of exposure to monkeys increased by more than 50%, most exposures to monkeys having occurred in enzootic zones [45]. The number of consultations following a fox bite did not significantly decrease despite the lack of risk after eradication of fox rabies in France (in 1998) and its borders. Furthermore, 60% (43/72) of patients received PEP in 2009 after contact with a fox in continental France, highlighting differences in practice not related to the epidemiology.

Exposure to small rodents (most often rats) still accounts for almost 2% of treatments 90% of which are related to exposures in continental France, even though these animals have never presented any risk of rabies transmission in France.

Furthermore, many treatments have been given following dog and cat bites for which monitoring by a veterinarian could not be implemented because even though the owners had been identified they had not complied with the mandatory monitoring of animals. Thus, it seems that the "biting animal monitoring" provides only little information to physicians making the decision to initiate PEP of not for a patient. It should be noted that all the rabid animals imported in France recently, except for the kitten in 2013, were identified during consultation with a veterinarian for a diagnosis, (because of symptoms), and not during the usual "biting animal monitoring".

The epidemiological context, in French Guiana, is specific because of vampire bat rabies, illustrated by the human case in 2008, because of common borders with countries where canine rabies is still endemic, and because of a great difficulty of access to PEP for populations living in the Amazon rain forest [46]. The 434 exposed patients having consulted and been treated in French Guiana, in 2011, were thus more frequently given PEP than in mainland France (55.8% of cases).

The observed therapeutic management is not always standardized. For example, many bitten patients (grade III) receive PEP, which means that the biting animal was considered at risk of transmitting rabies. The WHO recommends administrating both vaccination and immunoglobulins, in these cases, but this recommendation is applied only to less than 5% of patients in France. Indeed, between 2001 and 2009, 95% of the 28,000

patients having consulted and been treated after grade III contact with an animal other than a bat on continental France received anti-rabies vaccination but no serotherapy [43]. A mixed regimen between complete PEP (considering the risk as significant) and no PEP (considering the risk as insignificant) seems to be the current trend. This management would naturally not be ethical in enzootic zones or in case of proven contact with an animal coming from an enzootic zone. Indeed, if the anti-rabies vaccine administrated alone saves many lives even in case of grade III exposure, failures have been reported and the risk is even more significant when the prevalence of the disease is high.

Several hypotheses may be made to explain why no case of autochthonous rabies has been observed, with management of contacts not always complying with standardized recommendation:

The risk of rabies could have been null during that period because of:

- the absence of virus circulation (except for very rare cases related to a proven contact with a rabid animal illegally imported) or;
- a very weak circulation not causing human infection. With this hypothesis, more than 30,000 patients would have received useless vaccination, for an estimated cost of more than 5 million euros.

The risk of rabies, even if very weak, was real in some rare cases but the practice of vaccinating without immunoglobulins could have been sufficient to prevent any case (while avoiding treatment with human blood derived products for more than 30,000 patients).

These hypotheses cannot be checked or contradicted, without any marker proving the infected status or not of the animal, because it is impossible to correlate exposure, infection, PEP, and the outcome.

The current circumstances leading to a risk of human contamination in France are:

- the illegal importation of animals not complying with sanitary requirements (especially not vaccinated and not identified) incubating rabies (last case in October 2013 diagnosed on a kitten imported from Morocco);
- exposure in an enzootic zone, and onset of the disease after returning to France (1 case of human rabies imported from Gabon in October 2003, for example);
- contact with bats in continental France, the rabid epidemiology of which and the risk of human transmission are still badly documented (3 confirmed lethal human cases in Europe, none in France);
- Exposure to blood-feeding bat rabies or to domestic animals in French Guiana (1 case of human rabies in 2008).

In this new context, it seems important to analyze and better guide the current practices of anti-rabies medical centres. France still has among the highest rates of PEP in Europe despite the significant improvement of epidemiology [37]. No important decrease in the number of PEP was observed between 2001 and 2009, even though autochthonous rabies of non-flying mammals was eradicated. French recommendations should consequently be made for the management of exposed individuals in continental France and international recommendations should be adapted to the various epidemiological features in France.

8. Leads for improvement

8.1. Improve the estimation of risk of exposure to rabies

8.1.1. Origin of the animal

Any grade II or III exposure to an animal (susceptible to rabies) living in or coming from a confirmed rabid enzootic zone or a zone for which no information is available must be considered as at risk and treated as such (Table 3). This concerns individuals exposed in France to animals imported or having travelled – more or less recently – in an enzootic country as well as travellers (expatriates, tourists) bitten in enzootic countries. But, except for a possible period and zone of alert related to the importation of a case of rabies, a bite inflicted by a non-flying mammal, or one living in a rabies-free area according to the OIE criteria and not presenting any clinical symptoms suggesting rabies, is in principle not at risk of rabies.

8.1.2. Behaviour and status of the biting animal

The symptoms of rabies and the periods of incubation vary according to species. The duration of the period of virus excretion in saliva before onset of symptoms was determined in a very small number of animal species (mainly dogs, cats, ferrets, and foxes and a few experiments in bovines and sheep) [47–49]. In France, the duration of the observation period for suspect animals (15 days) is valid for non-flying mammals, mainly dogs, cats, and pet ferrets which are considered as normal by a veterinarian. The observation period for wild animals is extended to 30 days according to the available data on foxes.

A normal behaviour of the animal implicated at contact or an external cause of aggression cannot provide enough reliable information on the probability that it is infected or not by the rabies virus because of pre-symptomatic excretion. Furthermore, the definition of a normal or abnormal behaviour may be complicated for some wild species.

All bats are protected species in France and this may be an obstacle to their monitoring as biting animals. The pine marten (*Martres martres*) and the beech marten (*Martres foina*) have a more ambiguous status in France: they are partially protected by the April 29, 2008 decree which permanently bans all over continental France national their mutilation, their detention, transportation, stuffing, sale or purchase, commercial use or any other use. But they can still be hunted (June 26, 1987 decree) and may be classified as pests (September 30, 1988 decree).

8.1.3. The causative animal species

Several cases should be defined (Table 3).

The causative animal is a species that cannot be infected by a rabies virus (the case for birds). The animal (except for bats) lives or comes from a rabies-free zone and has not travelled to an enzootic zone or been in contact with an animal having travelled

Table 3
Current indications for PEP, according to animal species (only mammals are at rabid risk) and origin. This table was made according to the veterinarian monitoring system, implemented up in 2011.
Indications proposées de la prophylaxie post-exposition en fonction des espèces animales et de leur provenance (seuls les mammifères sont à risque rabique). Ce tableau a été établi en fonction du niveau de surveillance vétérinaire mis en place en 2011.

Domestic mammals	Origin/habitat	Proven contact with animals having travelled to an enzotic zone	Animal observation and/or possible biological tests	Therapeutic management
Dog	France	No	Yes	Wait
	France	Unknown	Yes	Wait
	France	Unknown	No	Grade II: type 1: no treatment type 2: vaccine alone or + Ig? Grade III: type 1: no treatment type 2: vaccine alone or + Ig? type 3: vaccine + Ig
	France	Yes	Yes or no	Wait or PEP depending of the delay between travel of the animal and patient exposure
	Enzootic zone	Not applicable	Yes or no	Stop PEP if results are negative
Cat and ferret	France	No	Yes	Wait
	France	No	No	No treatment
	France	Yes or unknown	Yes	Wait or PEP depending of the delay between travel of the animal and patient exposure
	France	Yes (Contact clearly identified)	No	Wait or PEP depending of the delay between travel of the animal and patient exposure
	Enzootic zone	Not applicable	Yes or no	Stop PEP if results are negative
Other domestic non carnivorous animals (cattle, horse, pigs)	France	No	Yes	No treatment
	France	Possible	Yes	Wait or PEP depending of the delay between travel of the animal and patient exposure and animal health status
	Enzootic zone	Yes or unknown	Yes	Wait or PEP depending of the delay between travel of the animal and patient exposure
Wild mammals	Origin/habitat	Proven contact with animals having travelled to an enzotic zone	Euthanasia and possible biological tests (Observation of these species is not adapted for the therapeutic decision)	Therapeutic management
Fox	France	Not applicable	Euthanasia or not and biological tests or not	No treatment
	Enzootic zone	Not applicable	Biological tests if possible	Stop PEP if results are negative
Other wild carnivores	France	No applicable	Euthanasia or not and biological tests or not	No treatment
	Enzootic zone	Not applicable	Biological tests if possible	Stop PEP if results are negative
Species other than carnivore and bats	France	Not applicable	Euthanasia or not and biological tests or not	No treatment
	Enzootic zone	Yes	Yes	Stop PEP if results are negative
	Enzootic zone	Yes	No	PEP
Bat	France	Yes	Yes	Wait if reliable results can be obtained in an acceptable delay
	Enzootic zone for non-flying animal rabies	Yes	No	PEP

to an enzootic zone (case of rodents and game in France). No treatment is necessary in these cases.

The causative animal is a species that can be infected by rabies and lives or comes from a rabid endemic zone for non-flying animals (staying abroad or animal known to have been recently imported from an enzootic zone). The WHO recommendations should be applied in these cases.

The causative animal is a species that can be infected by a rabies virus, but lives in continental France and has never left the country or the French overseas territories (except for French Guiana) or any other zone officially rabies-free zone for non-flying animals [44].

If the animal is available for observation: there is no reason to treat immediately if there are no symptoms suggesting rabies. If the biting animal presents with symptoms suggesting rabies, it becomes clinical suspected of rabies and it is then recommended to give PEP immediately. If treatment was already initiated, it can be stopped if the absence of rabies in the biting animal is confirmed. The certainty to have a laboratory answer in less than 7 days allows in some cases to delay using anti-rabies immunoglobulins.

Thus being bitten by a dog, cat, or autochthonous ferret not presenting with any signs of rabies should not result in systematic treatment. The veterinary observation of the biting domestic carnivore for 15 days is a legal obligation, it must be implemented when ever possible, with the help of the local sanitary authority (city-hall, military police, national police).

A person should not be treated immediately if the bite was inflicted by a wild animal (susceptible), captive or not (monkeys, rodents, foxes, game, etc.), when nothing suggests that they had stayed in an infected zone. Examining the animal head to look for rabid infection is a legal obligation if the biting animal, domestic or wild, dies during mandatory monitoring (duration of 30 days); it must be implemented whenever it is possible.

If the animal is not available for veterinarian monitoring or to be analyzed:

- dogs: given the possibility of illegal importation of a rabid dog and the possibility of transmission between dogs, 2 cases may be considered but there is no complete consensus:
  - it may be considered that, given the rarity of imported canine rabies cases in France and the capacity of the veterinarian network to identify these cases (the greatest number in Europe), PEP is not recommended and that this position will be reevaluated if clinical symptoms suggesting rabies appear or if there is evidence of illegal importation. This management has the advantage to be financially sparing and to save vaccines and Ig, and to avoid adverse effects, but it does not totally exclude the possibility of human rabies when the biting dog excretes rabid virus and was not detected as infected in due time,
  - conversely, it may be considered that despite very weak risk of undetected imported canine rabies, the lethality of the disease is 100%, thus PEP should be systematically recommended. The residual risk is extremely weak but it cannot be considered as totally null in continental France because of the porosity of borders with enzootic countries. This attitude has the advantage to offer the highest prevention of risk for human rabies, but its pertinence should be evaluated in a cost/benefit analysis benefice-risk in a country where rabies eradication is ongoing. Furthermore the cost-effectiveness of this highest prevention should be evaluated. In this case, cases of human rabies remain possible if an exposed individual does not consult, consults to late, or does not strictly comply with the management protocol;
- cats: some cases of cats illegally imported from an enzootic zone have been reported. Only 2 cases of rabies were reported in cats in France over the last few years; one was due to a bat virus, the other was an imported animal. This rarity does not support treating systematically. Finally, the risk of rabies related to an unknown travel of a cat to an enzootic zone is very weak compared to a dog;
- other wild non-flying animals (foxes, other carnivores, wild boars, rodents, hares, etc.): there is no reason to treat systematically, including for pine marten and beech marten except if the biting animal presented symptoms suggesting rabies, according to veterinarian observation, or if there was evidence of illegal importation;
- other domestic animals (ruminant, swine, equine, etc.): no PEP except if the animal comes or was in contact with an other animal coming from an enzootic zone, or if it presents suggestive clinical symptoms according to a veterinarian (in this case the animal should be killed and, except in very rare cases, treating or not with PEP can wait until obtaining the rabies NRC results)

Bat related cases: grade II or III exposure is an indication for PEP (including systematic vaccine + anti-rabies immunoglobulins in individuals not previously vaccinated) unless the bat cadaver can be analyzed in a reasonable delay.

8.2. *What modality should be used for PEP?*

In case of a bite by a dog that would be impossible to monitor, but outside of any importation from enzootic countries, 3 types of management may be considered according to the risk assessment:

- type 1: consider the risk of rabies as null in this case, in the current state of monitoring and distribution of epizootic, and consequently do not administrate any PEP whatever the grade of bites (position which should be reviewed if clinical signs suggesting rabies appear in the animal or if there is evidence of illegal importation);
- type 2: consider that there is a minimal but very severe risk, which should be taken into account and that the WHO recommendations should be applied (cf. Table 3), sometimes requiring the use of immunoglobulins;
- type 3: consider that the risk cannot be totally excluded but that it is weak and therefore the protection of the patient will only require vaccine (without adding immunoglobulins) whether the bite be grade II or III (this is currently the most common practice in France).

The rational for type I risk assessment is simple: the absence of risk considered implies the absence of treatment.

The rational for types II and III is the following: in case of grade III exposure, if treatment is necessary given the biting animal and the local epidemiology, the complete PEP treatment seems likely to be the most effective. The available published data, even if limited, seems to prove the superiority of the vaccine + immunoglobulins association compared to vaccine alone. The vaccine + IG association is recommended by the WHO for grade III exposures requiring PEP (given the epidemiology) and for grade II exposures occurring in immunodepressed individuals. The vaccine + IG association is recommended by the ACIP (Pasteur Institute Network) for grade II and III exposures. Since this association is acknowledged as the optimal treatment in terms of effectiveness, the prescription of an incomplete treatment (vaccine without Ig) in all circumstances where the risk is high enough to indicate a treatment, or the administration of vaccine alone would decrease the chances for a favourable outcome for the patient. An analogy can be made with blood exposure for which only complete treatment can be used, whatever the risk level, as soon as there is a risk.

Nevertheless, only local effectiveness can be expected of immunoglobulin, and so the absence of any visible lesion (an already ancient bite) would be the only element suggesting not administrating immunoglobulin.

9. Conclusion

Rabies in non-flying mammal is no longer present in France, except in imported cases, and does not justify using anti-rabies PEP systematically for all bitten patients.

PEP is indicated when there is a risk according to the epidemiology (travelling or importation), or clinical symptoms suggesting rabies in a cat or a dog, except when animal observation is possible. It may be justified to wait for monitoring results in some cases before initiating PEP or not.

PEP may be debated in 2 cases:

- should any person be treated systematically after having been bitten by a dog or a cat not available for monitoring? The circumstances of the bite can be used to decide only when the animal has a suspicious behaviour. A normal behaviour at the time of the bite does not rule out the risk. The risk is minimal, but not null;
- in case of a confirmed indication for treatment, should immunoglobulin be systematically associated to vaccinal injections? This association is known to be the most effective, compared to vaccination alone, and why restrict it to some patients, with the risk of decreasing the chances for a favourable outcome for the other patients?

For the time being, the decision must be made by the physician managing the bitten patient, since there are no official recommendations in France; and he must deal with the risk that an always lethal disease could occur in his patient.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Contribution of authors

All the authors contributed to the discussion, to drafting the initial text, and proofread the final version of the article.

JP Stahl wrote the final version of the article.

Acknowledgement

The authors are grateful to Dr Alexandra Mailles, French Institute for Public Health Surveillance, who helped gathering epidemiological data, and guidelines from other countries.

References

[1] W.H.O. Rabies vaccine: WHO position paper. Wkly Epidemiol Rec 2010;32(85):309–20.
[2] http://www.ictvonline.org/,. Consulté le 07/03/2014.
[3] Dodet B, Adjogoua EV, Aguemon AR, Baba BA, Bara Adda S, Boumandouki P, et al. The fight against rabies in Africa: from recognition to action. Vaccine 2009;27:5027–32.
[4] Knobel DL, Cleaveland S, Coleman PG, Fevre EM, Meltzer MI, Miranda ME, et al. Re-evaluating the burden of rabies in Africa and Asia. Bull World Health Organ 2005;83:360–8.
[5] Holmes EC, Woelk CH, Kassis R, Bourhy H. Genetic constraints and the adaptive evolution of rabies virus in nature. Virology 2002;292:247–57.
[6] Bourhy H, Reynes JM, Dunham EJ, Dacheux L, Larrous F, Huong VT, et al. The origin and phylogeography of dog rabies virus. J Gen Virol 2008;89:2673–81.
[7] Lonova GN, Belikov SI, Kondratov IG, Krylova NV, Pavlenko EV, Romanova EV, et al. A fatal case of bat lyssavirus infection in primorye teritory of the Russian Far East Rabies. Bull Eur 2009;33:5–8.
[8] http://www.who.int/rabies/rabies_maps/en/,. Consulté le 07/03/2014.
[9] http://apps.who.int/globalatlas/default.asp/,. Consulté le 07/03/2014.
[10] http://web.oie.int/wahis/public.php?page=home,. Consulté le 07/03/2014.
[11] http://www.rbe.fli.bund.de/,. Consulté le 07/03/2014.
[12] De Benedictis P, Gallo T, Lob A, Coassin R, Squecco G, Ferri G, et al. Emergence of fox rabies in north-eastern Italy. Euro Surveill 2008;13:1–2.
[13] Tsiodras S, Dougas G, Baka A, Billinis C, Doudounakis S, Balaska A, et al. Re-emergence of animal rabies in northern Greece and subsequent human exposure. October 2012–March 2013. Euro Surveill 2013;18:20474.
[14] Bourhy H, Dacheux L, Strady C, Mailles A. Rabies in Europe 2005. Euro Surveill 2005;10:213–6.
[15] Gautret P, Ribadeau-Dumas F, Parola P, Brouqui P, Bourhy H. Risk for Rabies Importation from North Africa. Emerg Infect Dis 2011;17(12):2187–93.
[16] Floret D, Bourhy H, Peigue-Lafeuille H. Don't forget rabies! Med Mal Infect 2005;35(S2):S112–3.
[17] Mahamat A, Meynard JB, Djossou F, Dussart P, Demar M, Fontanella JM, et al. Risk of rabies transmission and adverse effects of postexposure prophylaxis in health care workers exposed to a fatal case of human rabies. Am J Infect Control 2012;40(5):456–8.
[18] Meynard JB, Flamand C, Dupuy C, Mahamat A, Eltges F, Queuche F, et al. First human rabies case in French Guiana, 2008. Epidemiological investigation and control. PLoS Negl Trop Dis 2012;6:e1537.
[19] Berger F, Desplanches N, Baillargeaux S, Joubert M, Miller M, Ribadeau-Dumas F, et al. Rabies risk: difficulties encountered during management of grouped cases of bat bites in 2 isolated villages in French Guiana. PLoS Negl Trop Dis 2013;27:e2258.

[20] French multidisciplinary investigation team. Identification of a rabid dog in France illegally introduced from Morocco. Euro Surveill 2008;13 [pii:8066].
[21] Dacheux L, Larrous F, Mailles A, Boisseleau D, Delmas O, Biron C, et al. European bat lyssavirus transmission among cats, Europe. Emerg Infect Dis 2009;15:280–4.
[22] Dupuy C, Berger F, Baudrimont X, Martrenchar A, Moutou F, Spiegel A, et al. Situation de la rage animale en Guyane. Bull Epidemio Anses 2011;BE43:26–30.
[23] Bordas V, Meyer-Broseta S, Bénet JJ, Vazquez MP. Étude descriptive des morsures caninies chez les enfants: analyse de 237 cas enregistrés aux urgences de l'hôpital Trousseau (Paris). Epidemiol Sante Anim 2002;42:115–21.
[24] Lavaud J, Vazquez M, Bordas V, Duval C. Animaux domestiques et accidents chez l'enfant. Arch Pediatr 2005;12:228–33.
[25] Thélot B, Ricard C. http://www.invs.sante.fr/
[26] Lang ME, Klassen T. Dog bites in Canadian children: a five-year review of severity and emergency department management. CJEM 2005;7:309–14.
[27] Anon. Nonfatal dog bite-related injuries treated in hospital emergency departments-United States, 2001. MMWR Morb Mortal Wkly Rep 2003;52:605–10.
[28] Weiss HB, Friedman DI, Coben JH. Incidence of dog bite injuries treated in emergency departments. JAMA 1998;279:51–3.
[29] Tan RL, Powell KE, Lindemer KM, Clay MM, Davidson SC. Sensitivities of three county health department surveillance systems for child-related dog bites: 261 cases (2000). J Am Vet Med Assoc 2004;225:1680–3.
[30] Schalamon J, Ainoedhofer H, Singer G, Petnehazy T, Mayr J, Kiss K, et al. Analysis of dog bites in children who are younger than 17 years. Pediatrics 2006;117:e374–9.
[31] De Keuster T, Lamoureux J, Kahn A. Epidemiology of dog bites: a Belgian experience of canine behaviour and public health concerns. Vet J 2006;172:482–7.
[32] Ostanello F, Gherardi A, Caprioli A, La PL, Passini A, Prosperi S. Incidence of injuries caused by dogs and cats treated in emergency departments in a major Italian city. Emerg Med J 2005;22:260–2.
[33] Kahn A, Bauche P, Lamoureux J. Child victims of dog bites treated in emergency departments: a prospective survey. Eur J Pediatr 2003;162:254–8.
[34] Bourhy H, Lafon M, Berthonneau MC, Renner Y, Rollin PE, Sureau P. Rabies in vaccinated dogs in Gabon. Vet Rec 1988;122:361–2.
[35] http://www.who-rabies-bulletin.org/about_rabies/Prevention_Humans.aspx
[36] Bourhy H, Dacheux L, Ribadeau-Dumas F. The use of passive rabies immunotherapy: from the past to the future. Biol Aujourdhui 2010;204: 71–80.
[37] Bourhy H, Goudal M, Mailles A, Sadkowska-Todys M, Dacheux L, Zeller H. Is there a need for anti-rabies vaccine and immunoglobulins rationing in Europe? Euro Surveill 2009;14 [pii: 19166].
[38] Dodet B, Goswami A, Gunasekera A, de Guzman F, Jamali S, Montalban C, et al. Rabies awareness in eight Asian countries. Vaccin 2008;26: 6344–8.
[39] Si H, Guo ZM, Hao YT, Liu YG, Zhang DM, Rao SQ, et al. Rabies trend in China (1990–2007) and post-exposure prophylaxis in the Guangdong province. BMC Infect Dis 2008;21(8):113.
[40] Dimaano EM, Scholand SJ, Alera MT, Belandres DB. Clinical and epidemiological features of human rabies cases in the Philippines: a review from 1987 to 2006. Int J Infect Dis 2011;15:e495–9.
[41] Gong Z, He F, Chen Z. Risk Factors for Human Rabies in China. Zoonoses Public Health 2012;59(1):39–43.
[42] Shantavasinkul P, Wilde H. Postexposure prophylaxis for rabies in resource-limited/poor countries. Adv Virus Res 2011;79:291–307.
[43] www.pasteur.fr/ip/resource/filecenter/document/01s-00004j-0gi/bulletin-2011.pdf,. Consulté le 07/03/2014.
[44] www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1259152458758,. Consulté le 07/03/2014.
[45] Gautret P, Blanton J, Dacheux L, Ribadeau-Dumas F, Brouqui P, Parola P, et al. Rabies in nonhuman primates and potential for transmission to humans: a literature review and examination of selected French national data. PLoS Negl Trop Dis 2014;8(5):e2863.
[46] Berger F, Desplanches N, Baillargeaux S, Joubert M, Miller M, Ribadeau-Dumas F, et al. Difficulties encountered during management of grouped cases of bat bites in 2 isolated villages in French Guiana. PLoS Negl Trop Dis 2013;7(6):e2258.
[47] Wandeler A, Wachendörfer G, Förster U, Krekel H, Müller J, Steck F. Rabies in carnivores in central Europe-II virological and serological examinations. Zbl Vet Med B 1974;21:757–64.
[48] Selimov M, Tatarov A, Ilyasova R, Onikhimovskaya V. Problems of natural foci of sylvatic and arctic rabies. Rabies Bull Eur 1980;4:12–5.
[49] Matouch O. Distribution of rabies virus in the central nervous system of naturally infected foxes. Vet Med Praha 1978;23:369–76.