Is there a need for anti-rabies vaccine and immunoglobulins rationing in Europe?

H Bourhy (hbourhy@pasteur.fr)[1], M Goudal[1], A Mailles[2], M Sadkowska-Todys[3], L Dacheux[1], H Zeller[4]
1. WHO Collaborative Center for Reference and Research on Rabies, National Reference Centre for Rabies, Institut Pasteur, Paris, France
2. Institut de veille sanitaire, Saint-Maurice, France
3. National Institute of Public Health, Warsaw, Poland
4. Preparedness and Response Unit, European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

Rabies is a lethal encephalitis caused by a lyssavirus and transmitted from animals to humans via bite wound, scratch wound, or licking of mucous membranes. It is preventable by timely administration of post-exposure prophylaxis (PEP) consisting of four or five doses of rabies vaccine combined, in the most severe cases of exposures, with anti-rabies immunoglobulin (RIG). Although the rabies incidence in humans remains low, rabies is still present in some European countries. Moreover, rabid animals imported from enzootic areas are reported every year in rabies-free areas. These importations threaten the rabies-free status of terrestrial animals in western European countries and challenge the public health surveillance system and the health structures responsible for rabies prophylaxis and control. The importations frequently result in the prescription of a large number of PEP including RIG, especially in western European countries. The situation is inverted in some central and eastern European countries where RIG is underprescribed. Only a limited number of rabies vaccines and particularly of RIG are licensed for use in Europe. Their availability is also limited, a situation that may become worse in the future. It therefore seems important to study the possibility of comparing and unifying national PEP guidelines in Europe, if needed, and to generate effective solutions in the event of a shortage of anti-rabies biological products and RIG in particular, such as rationing these products.

Introduction

Rabies is a lethal encephalitis caused by a lyssavirus which is transmitted from animals to humans via bite wound, scratch wound, or licking of mucous membranes [1]. Human-to-human transmission has not been proven. However, some cases of rabies transmission through organ transplantation have been described [2,3]. Since Louis Pasteur's discovery of the rabies vaccine, rabies has been a disease that can be prevented through the timely administration of post-exposure prophylaxis (PEP). Today, PEP consists of four or five doses of rabies vaccine administered on three to five visits. Anti-rabies immunoglobulin (RIG) is given in addition, if the exposure fulfils the criteria of Category III as defined by the recommendations given by the World Health Organization (WHO) [4,5].

Rabies is still present on the European continent, although some countries have rabies-free status according to the criteria of the World Organisation for Animal Health (OIE). Its incidence in humans remains low (fewer than five human cases per year) owing to the strict application of PEP and to veterinary rabies control measures in domesticated and wild animal populations.

The main indigenous animal reservoirs are dogs in eastern European countries and on the borders with the Middle East, foxes in central and eastern Europe, racoon dogs in north-eastern Europe and insectivorous bats throughout the entire territory [6]. In addition, cases of rabid animals imported from enzootic areas outside Europe are reported every year, which shows the permeability of borders and travellers' lack of awareness of the rabies risk [7]. These importations constantly threaten the rabies-free status of terrestrial animals in western European countries. The associated risk also complicates the decision concerning human PEP when the biting animal is not accessible for rabies assessment (clinical examination and/or laboratory examination) [6,8]. In view of the complexity of rabies epidemiology in the European Union (EU), it is important to keep health professionals, particularly physicians and veterinarians, updated in order to maintain vigilance. Recommendations to improve rabies control in animals and prevention of human transmission have recently been published in the WHO Expert Consultation on Rabies [4].

The objective of this paper is to review the current situation in the EU countries regarding the needs for rabies vaccine and anti-rabies immunoglobulins as well as the risk of a potential shortage, using as examples the current practice in France and in Poland.

Different usage of rabies biological products in Europe

Data on the use of rabies vaccine and anti-rabies immunoglobulin and on the number of PEP in Europe are scarce. Therefore, we will mainly focus our report on two countries, France and Poland, that have implemented centralised surveillance.

In France, data from 2007 showed that 3,631 people (47% of all people who sought medical care in anti-rabies centres) received PEP treatment with 11% of them receiving RIG. In February 2008, two cases of autochthonous rabid dogs lead to the prescription of

241 PEP in people who had been bitten, 34 of whom also received RIG, in accordance with the French and WHO recommendations. The index case was a dog illegally imported from Morocco [9]. Following this event, France lost its rabies-free status according to the OIE criteria. Since then, no other case of canine or feline rabies have been diagnosed in non-travelling animals, which makes us confident that the veterinary control measures taken after the incident have been effective in controlling further spread of the virus. In November 2008, a rabid dog imported to France from Spain was identified. The three month-old animal was found to be infected by a strain phylogenetically very close to those circulating in Morocco, indicating a potential recent importation from Morocco (unpublished results). Of 32 people who were in contact with this dog, seven received PET including vaccine and RIG, 18 received vaccine only and the remaining seven people were not considered at risk and therefore did not receive any PET. Unfortunately, such episodic importations of rabies-infected dogs are not rare. Between 2000 and 2008, seven rabid dogs had been illegally imported into France from Africa. For each imported rabid dog, between two and 187 people with direct contact had received post-exposure vaccination, and nearly 15% of them had also received anti-rabies immunoglobulin.

Several other rabies-free countries in Europe have also reported importation of rabid animals in the past (e.g. Belgium, Switzerland, and the United Kingdom). These episodes further supported the recommendation of prescribing PEP for patients bitten by a dog of unknown origin or suspected to come from an enzootic country. The recent re-emergence of fox rabies in Italy has stressed further that rabies in non-flying wildlife is not completely under control in Europe and that it can re-infect areas from which it was eliminated years before [10]. Consequently, the periodical re-introduction of rabies in any of the EU countries has an immediate impact on the number of PEP interventions, i.e. the number of rabies vaccine and immunoglobulin doses used in EU.

The number of reported human exposures to bats in Europe has also increased in recent years. In these cases, patients received RIG together with the vaccine in accordance with national and WHO guidelines [4]. In France alone, an average of 100 people receive PEP including RIG after exposure to bats every year.

On the other hand, RIG may be underprescribed in some countries in central and eastern Europe. In Poland, for example, PEP is administered to about 7,000 people every year (54,767 patients in total during the period from 2001 to 2007), and only 0.8% of these patients also receive RIG. In the same time period, 644 individuals received PEP after a contact with bats and only 4.7% of them received RIG. In these countries, a strict application of WHO guidelines would therefore immediately lead to an increase in the use of RIG in particular.

Risk of vaccine shortage

According to the number of rabies vaccine sold every year and in the absence of more precise data, we can estimate that world-wide, at least 15 million PEP are administered annually. The EU, the United States (US) and Canada only represent 1% of the global consumption. European producers have implemented high quality control standards for the production of rabies vaccines and immunoglobulin. The two European producers supply about 25% of the rabies vaccine doses used annually worldwide.

An official health advisory report published in June 2008 by the US Centers for Disease Control and Prevention (CDC) indicated a temporary decrease in human rabies vaccine supplies in the US [11,12]. The two European producers (Sanofi Pasteur and Novartis) are the only suppliers of rabies vaccine for the use in humans in the US. Supplies of rabies vaccine went down in the US after Sanofi Pasteur started renovations in the French production facility for the IMOVAX rabies vaccine (produced on human diploid cells) in June 2007, and after Novartis had to suspend its supply to the US and the EU in September 2007 following an inspection conducted by the US Food and Drug Administration (FDA) (http://www.fda.gov/foi/warning_letters/archive/s6644c.pdf). The renovations conducted by Sanofi Pasteur are expected to be completed by mid-2009 and the registration of IMOVAX (the rabies vaccine produced in this facility) by the end of 2009. Novartis started building a new rabies vaccine production facility in Germany in May 2008. It is expected to be fully operational in 2011 [11,13].

As a consequence, the US CDC strongly recommend that healthcare providers, public health authorities at state and local level, animal control officials, as well as the public take immediate steps to ensure appropriate use of human rabies biological products. The US CDC stressed that the judicious and appropriate use of rabies vaccine is crucial in order to avert a situation that puts individuals exposed to rabies at increased risk due to depleted vaccine supplies [13]. Therefore the use of rabies vaccine is restricted to situations meeting the criteria indicated in the recommendations [13]. Regarding pre-exposure prophylaxis in the US, priority is given to those at greatest risk of rabies exposure (e.g. people working in rabies laboratories, animal control officers, veterinary staff or wildlife workers), taking into consideration the available rabies vaccine supplies. For groups at lower risks of exposure (e.g. travellers and veterinary students), the US CDC proposes to suspend pre-exposure prophylaxis until the vaccine supply levels are restored.

The availability of rabies vaccines in Europe differs from that in North America where only vaccines produced in chicken embryo cell culture or human diploid cells are licensed. In Europe, vaccine is produced in Vero cells in large amounts and widely used in Europe, particularly in France, as well as in Asia and Africa. It represents a possible alternative in the event of a shortage of the two other products.

Risk of RIG shortage

The stock of specific human RIG is more limited and it has been known for some time that there is a world-wide shortage [14]. Only three to five million doses of anti-rabies immunoglobulin are produced and sold every year. Considering that the number of doses used in one protocol of PEP varies according to the patient's weight in kg, no more than an estimated 2-5% of patients seeking PEP can have received anti-rabies immunoglobulin. The current level of production does not cover the needs. According to WHO estimates, about 60% of the people seeking care for PEP do not receive an injection of anti-rabies immunoglobulin, although they fall into the category of exposure that would require it [4,15,16]. This is mainly due to difficulties with access to this biological product, but also to limited production compared to the world-wide demand. In Europe, two types of purified anti-rabies immunoglobulin are produced, human (HRIGs) and equine (ERIGs). The entire production of HRIGs, which is limited due to the lack of plasma donors, is almost exclusively sold in the US and Europe. Therefore any increase

in demand may cause problems. However, ERIGs are now highly purified, well tolerated and have been demonstrated to be efficient in post-exposure treatment [17]. They are produced in large amounts and may be a suitable alternative in case of a shortage of HRIG, although they have not yet been licensed in Europe. Other products of good efficacy and safety manufactured outside Europe could also be used as a complementary source of supply. Cocktails of monoclonal antibodies have also been recently developed for this purpose [18]. Although promising, the first licence of this type of product cannot be expected before 2012 or 2013.

Discussion

In France and Poland, recommendations for rabies PEP (both vaccine and immunoglobulin) followed national guidelines and/or WHO guidelines which recommend that people should receive PEP when bitten by an animal suspected to be infected by rabies. Clinicians make an individual risk assessment for each patient bitten or scratched, and decide to administer rabies vaccine with or without immunoglobulins according to the general recommendations, epidemiological data and the category of the bite. The veterinary situation is taken into account in this assessment, namely the species of the biting animal and the possibility of carrying out examination of the animal if it can be identified. Although no study has investigated the actual prescription practices, it is suspected that some PEP prescriptions are not based on the guidelines [19]. In Europe, practices vary, relying either on special anti-rabies centres (such as in France) or on private general practices (such as in Germany). Furthermore, there seems to be large variations in the use of PEP and especially RIG between European countries, with some countries overreacting (for example France) and others underprescribing (like Poland). Therefore, it would be important to review and analyse practices in the EU, as has been done in North American countries [20].

The risk of a potential shortage of rabies vaccine seems limited in Europe. However, it is important to note that the risk of a potential shortage of RIG in the event of an unplanned increase in demand or a limitation in supply is shared by many countries in Europe and other continents [8,21-23]. The availability of other RIG that have proved their efficacy and safety and that are presently not widely licensed in this area constitutes a possible alternative.

Note added in proof

Since the time of submission of this paper, an European consultation was conducted at the European Centre for Disease Prevention and Control (ECDC) in Stockholm on 15 January 2009. The group of experts gathered at this occasion further emphasised the need to review the rabies epidemiological situation in Europe. It also recommended to map practices and usage of anti-rabies biological products in Europe in order to be able to propose effective options for optimisation, as has been done for other vaccines [24]. The conclusions of this meeting will be available from ECDC.

References

1. Hemachudha T, Laothamatas J, Rupprecht CE. Human rabies: a disease of complex neuropathogenetic mechanisms and diagnostic challenges. Lancet Neurol. 2002;1(2):101-9.
2. Hellenbrand W, Meyer C, Rasch G, Steffens I, Ammon A. E-alert 18 February: Cases of rabies in Germany following organ transplantation. Euro Surveill. 2005;10(8):pii=2917. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=2917
3. Jackson AC. Rabies: new insights into pathogenesis and treatment. Curr Opin Neurol. 2006 Jun;19(3):267-70.
4. WHO Expert Consultation on rabies. World Health Organ Tech Rep Ser. 2005;931:1-88, back cover.
5. Rabies Vaccines. WHO position paper. Wkly Epidemiol Rec. 2007;82(49/50):425-35.
6. Bourhy H, Dacheux L, Strady C, Mailles A. Rabies in Europe in 2005. Euro Surveill. 2005;10(11):pii=575. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=575
7. Servas V, Mailles A, Neau D, Castor C, Manetti A, Fouquet E, et al. An imported case of canine rabies in Aquitaine: investigation and management of the contacts at risk, August 2004-March 2005. Euro Surveill. 2005;10(11):pii=578. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=578
8. Gautret P, Soula G, Adamou H, Soavi MJ, Delmont J, Rotivel Y, et al. Rabies postexposure prophylaxis, Marseille, France, 1994-2005. Emerg Infect Dis. 2008;14(9):1452-4.
9. French multidisciplinary investigation team. Identification of a rabid dog in France illegally introduced from Morocco. Euro Surveill. 2008;13(11):pii=8066. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8066
10. De Benedictis P, Gallo T, Iob A, Coassin R, Squecco G, Ferri G, et al. Emergence of fox rabies in North-Eastern Italy. Euro Surveill. 2008;13(45):pii=19033. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19033
11. Reserves of human-use rabies vaccine could alleviate supply worries. JAVMA News. 2008, September 15. American Veterinary Medical Association. Available from: http://www.avma.org/onlnews/javma/sep08/080915a.asp
12. Rabies vaccine supply situation. [Accessed 11 March 2009]; Atlanta: Centers for Disease Control and Prevention; 2009 February 6. Available from: http://www.cdc.gov/rabies/news/RabVaxupdate.html
13. Manning SE, Rupprecht CE, Fishbein D, Hanlon CA, Lumlertdacha B, Guerra M, et al. Human rabies prevention--United States, 2008: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep. 2008;57(RR-3):1-28.
14. Haupt W. Rabies--risk of exposure and current trends in prevention of human cases. Vaccine. 1999;17(13-14):1742-9.
15. Dodet B, Africa Rabies Expert Bureau (AfroREB), Adjogoua EV, Aguemon AR, Amadou OH, Atipo AL, et al. Fighting rabies in Africa: The Africa Rabies Expert Bureau (AfroREB). Vaccine. 2008;26(50):6295-8.
16. Dodet B, Goswami A, Gunasekera A, de Guzman F, Jamali S, Montalban C, et al. Rabies awareness in eight Asian countries. Vaccine. 2008;26(50):6344-8.
17. Quiambao BP, Dytioco HZ, Dizon RM, Crisostomo ME, Laot TM, Teuwen DE. Rabies Post-Exposure Prophylaxis in the Philippines: Health Status of Patients Having Received Purified Equine F(ab')(2) Fragment Rabies Immunoglobulin (Favirab). PLoS Negl Trop Dis. 2008;2(5):e243.
18. Bakker AB, Python C, Kissling CJ, Pandya P, Marissen WE, Brink MF, et al. First administration to humans of a monoclonal antibody cocktail against rabies virus: safety, tolerability, and neutralizing activity. Vaccine. 2008;26(47):5922-7.
19. Peigue-Lafeuille H, Bourhy H, Abiteboul D, Astoul J, Cliquet F, Goudal M, et al. [Human rabies in France in 2004: update and management]. Med Mal Infect. 2004;34(12):551-60. [In French].
20. Huot C, De Serres G, Duval B, Maranda-Aubut R, Ouakki M, Skowronski DM. The cost of preventing rabies at any cost: post-exposure prophylaxis for occult bat contact. Vaccine. 2008;26(35):4446-50.
21. Albouy-Llaty M, Le Moal G, Bouche G, Dupuis A, Becq-Giraudon B, Migeot V. [Imogam rage prescription assessment in the rabies prophylaxis center of Poitiers]. Med Mal Infect. 2007;37(2):108-11. [In French].
22. Moran GJ, Talan DA, Mower W, Newdow M, Ong S, Nakase JY, et al. Appropriateness of rabies postexposure prophylaxis treatment for animal exposures. Emergency ID Net Study Group. Jama. 2000 23-30;284(8):1001-7.
23. Sadkowska-Todys M, Łabuńska E.. [Rabies in Poland in 2002]. Przegl Epidemiol. 2004;58(1):143-52. [In Polish]
24. Uscher-Pines L, Barnett DJ, Sapsin JW, Bishai DM, Balicer RD. A systematic analysis of influenza vaccine shortage policies. Public Health. 2008;122(2):183-91.

This article was published on 2 April 2009.

Citation style for this article: 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(13):pii=19166. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19166