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Review Article

Global Financial Crisis as a Challenge for Prevention of Human Rabies in the Former Soviet Republics

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Abstract

Prevention and control of rabies remains a pressing problem in the least developed and developing countries of Eurasia. In many of them, this problem is largely due to financial deterrents. Among these, the chronic shortage of funds for early detection, prompt diagnosis and adequate prophylaxis of animal rabies has serious consequences for public health. Today, this problem is acutely felt in the Former Soviet Union (FSU) area, where countries are still in the process of recovery from previous and current economic shocks. With the onset of the global financial crisis, the epidemiological situation with rabies in the FSU area has worsened, which was reflected in dozens of human deaths over the past five years. To improve early detection of rabies in humans, the Institut Pasteur du Cambodge (IPC) has developed a method of rapid ante-mortem diagnosis of human rabies, which can be used by public health authorities as a tool to increase effectiveness of disease case management and to raise awareness of their governments about the risk posed by this infection to human health and life.

Keywords: Human rabies; Zoonotic diseases; Former soviet union; Pre-exposure prophylaxis

Introduction

For more than three millennia, rabies has been known as one of the most feared human diseases. Today, it is widely distributed across the globe, with only a few countries (mainly islands and peninsulas) that are free of the disease. Rabies ranks first in the list of neglected zoonotic diseases, targeted for regional and eventual global elimination [1]. According to most recent analyses, each year, rabies causes 74,000 human deaths around the world; more than 95% of them occur in Asia and Africa [2]. As of 2005, rabies was enzootic throughout the whole territory of Eurasia, where cycles of circulation of the virus were established in dogs, wild carnivores and insectivorous bats. These cycles are quite independent, because of the strong barrier that between species-adapted rabies viruses and various potential hosts [3]. In the FSU area of Eurasia, the rabies virus is represented by five phylogenetic groups of isolates, namely: 1) Arctic group; 2) Central Russian group; 3) Eurasian group; 4) Northern European group; and 5) Caucasian group [4]. New field isolates of the virus, detected in 2008-2011 in various parts of the FSU area placed into phylogenetic groups described before [5]. In 2004-2014, measures towards prevention and control of rabies were implemented in all the FSU republics, but only in three of them (Latvia, Lithuania and Estonia) were tangible results achieved as of 2015 [6-8]. Information about occurrence of animal and human rabies in other FSU republics is very scarce; however evidence suggests that in 2013-2014 this disease from time to time has affected animals and humans in a majority of the republics.

Methods

This study uses a descriptive epidemiological analysis based on a combination of desktop review of retrospective and operative information about the occurrence of human rabies in the FSU republics and analysis of options for reducing the mortality of humans from rabies. The information was collected through a literature search, screening of technical documents and interviews with representatives of the national animal health and public health authorities. The literature search was focused on available technical documents about epidemiological patterns of rabies in the FSU area that were published over the period from 2004 to 2015 and restricted to English and Russian languages. The information was retrieved from bulletins of the Office International des Epizooties (OIE), World Health Organization (WHO) and Global Alliance for Rabies Control (CARC), reports of the Food and Agriculture Organization of the United Nation (FAO) and Middle East and Eastern Europe Rabies Expert Bureau (MEEREB) and statistics provided by veterinary and public health authorities of the FSU republics. The retrieved information was analyzed in comparison with data collected in the FSU republics over the period from 2010 to 2015 and reported by the FSU republics to the WHO Rabies Information System (RIS), OIE World Animal Health Information System (WAHIS) and Federal Center for Animal Health of Russian Federation (ARRIAH) in 2014.

Results

The available information suggests that animal and human rabies occur in the overwhelming majority of FSU republics, moreover in some of them this disease causes human deaths almost every year. According to WAHIS and ARRIAH data, in 2014 human rabies was reported in Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan and the Russian Federation. Except for in the Russian Federation, all reported cases of human rabies were fatal. No information has been reported from Armenia, Belarus, Estonia, Latvia, Lithuania, Moldova, Tajikistan, Turkmenistan, Ukraine and Uzbekistan. Given the results achieved in controlling rabies in Estonia, Latvia and Lithuania, the

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absence of reports from these countries could be treated as logical. This cannot be said about the other FSU republics, where rabies still occurs in dogs, cats and other domestic animals. For example, it is known that canine rabies occurs in Turkmenistan and Uzbekistan [9], but information on incidence of human rabies in these countries over the past 10 years is not available. While the main reason for the absence of reports from Uzbekistan is that human rabies is not a notifiable disease in this country [10], we can only guess the reason for the lack of information from Turkmenistan, where rabies is in the list of notifiable diseases. In Tajikistan, the last report on incidence of human rabies was submitted by the national veterinary authority to OIE WAHIS in 2011, while the available data suggests that 24 cases of human rabies were confirmed in the country over the period from 2012 to 2015. According to media reports, the public health authority of Tajikistan confirms on average 10 to 20 cases of human rabies annually [11].

The lack of reliable information is one of the main barriers to effective prevention and control of human rabies not only at global and regional levels, but also at the national level. This is largely due to the chronic shortage of resources for routine surveillance, early detection and prompt diagnosis of rabies, continuously experienced by veterinary and public health services in the FSU republics. Today, well-equipped laboratories operate at central level in almost all the FSU republics but, due to lack of diagnostic kits and reagents, only some of them can afford routine use of Enzyme-Linked Immunosorbent Assay (ELISA) and Polymerase Chain Reaction (PCR) for diagnosis of human rabies. The latter is largely based on Fluorescent Antibody Test (FAT), which is the only method that allows identifying virus-specific antigen in a short time and at a reduced cost [12]. Other diagnostic techniques that are used for diagnosis of human rabies in the FSU republics include the Tissue Culture Infection Test (TCIT), Mouse Inoculation Test (MIT) and histopathological examination. The latter is no longer recommended by the WHO, but in the absence of alternatives it is still used by regional and district laboratories in some of the FSU republics which are not technical capable of conducting FAT, TCIT and MIT. The available information suggests that in most of the FSU republics, people seeking for medical intervention after exposure to an animal are admitted to Post-Exposure Prophylaxis (PEP) for rabies without diagnosis and are obliged to endure protracted anxiety unless they receive it. This causes unnecessary use of the life-saving vaccine, which can result in its absence in cases when the administration of PEP is necessary.

Discussion

As of 2005, urban rabies was considered predominant in the Caucasian and Asian parts the FSU, while sylvatic rabies predominated in the European part [4]. Over the next decade, the geographical spread of rabies in the FSU area has not undergone significant changes, but the epidemiological situation as regards rabies in Estonia, Latvia and Lithuania has tangibly changed: a combination of Pre-Exposure Prophylaxis (PrEP) of the disease in animals and its PEP in humans have resulted in the elimination of human rabies. In the rest of FSU republics, the administration of PEP has not been successful in preventing all cases of human rabies, and fatalities have persisted. For example, in Ukraine, wherein 2009-2011 the average number of victims of animal bites was 2025 per annum with 0.10 incidence of human rabies and administration of 440 PEP per million inhabitants, the mortality of humans from the disease in 2014 was 0.09 per million inhabitants [13,14]. Moreover, each year about 20000 people in Ukraine seek medical intervention after a bite, but PEP is actually required only for one in five [15]. In Georgia, in 2009-2011, the average number of animal bite victims was 9,780 with a 0.29 incidence of human rabies and administration of 7400 PEP per million inhabitants, but the mortality of humans from the disease in 2014 was 0.8 deaths per million inhabitants. Therefore, over the period from 2009 to 2015, in Georgia PEP was administered by 74 designated medical centers and covered 82% of reported victims of animal bites, while in Ukraine PEP was provided by 29 centers and covered only 21% of victims respectively [13,14].

The example of Georgia and Ukraine suggests that the information reported by these countries should not be taken at face value, as there are several factors that may affect population-based results of PEP in the country. For example, in Georgia, over the period 2009-2011 the incidence of PEP increased by more than 15%, but these figures contained the total number of PEP provided to animal bite victims. Only a quarter of initiated PEP courses were completed, while the rest were ceased after the 10-day-observation of animals suspected of being rabid [15]. In terms of results achieved in population-based PEP of human rabies, Kazakhstan occupies an intermediate position between Ukraine and Georgia. In 2009-2011 the average number of animal bite victims in Kazakhstan was 3915, and the incidence of human rabies was 0.6 and 3737 PEP per million inhabitants, administered by 250 designated centers. Over the reporting period, PEP was administered to more than 98% of reported victims of animal bites [13]. Similarly to Georgia, in Kazakhstan the number of PEP administered in 2011 increased by about 15% in comparison to 2009, and was equal to 0.4% of the country population [15]. Despite considerable resources devoted to PEP, at the end of 2014 the mortality of humans from rabies in Kazakhstan was0.17per million inhabitants. The example of Ukraine, Georgia and Kazakhstan demonstrates that as regards PEP of human rabies, information reported by the public health authorities of the FSU republics is incomplete and takes no account of factors that may affect the likelihood of promptly obtaining and completing a vaccination course.

Prompt access to PEP is essential for prevention of human death from rabies [16]. In most of the FSU republics PEP the policy of prevention of human rabies is based on free of charge provision of PEP to all admitted patients. This approach, however, is unable to reduce the risk of rabies, as there are many factors that hinder access to PEP or its prompt administration. According to ARRIAH, in 2014in the Russian Federation more than 371,000 people were exposed to animals, but human deaths was prevented through administration of PEP on time. According to WHO RIS, no cases of human rabies were recorded in Belarus and Moldova [17]. In Armenia, administration of PEP enabled a reduction in the number of human deaths from rabies from 2-3 in 2006-2009 to 0 in 2010-2012. According to the public health authority of Armenia, in 2014 the number of animal bite victims was 2,700, but due to administration of PEP, human deaths from rabies were avoided. However, free provision of PEP does not always prevent avoidable human deaths from rabies. The OIEWAHIS data shows that, during 2014, rabies caused 6 human deaths in

Kazakhstan, 4 in Georgia, 4 in Azerbaijan and 1 case in Kyrgyzstan. In all these republics, PEP is provided free of charge but, due to scarcity and/or remoteness of designated medical centers, admitted patients are often unable to receive and/or complete the course of treatment. Therefore, barriers that may prevent timely access to PEP or may cause dangerous delays with it (e.g. location of designated medical centers, weather conditions, availability of transport etc.) should be considered.

In some FSU countries, governments provide vaccine free-of-charge or subsidize its cost, but budgets allocated for this are often insufficient, resulting in shortages or leaving only a few centers with a reliable supply of PEP. In some of them the administration of PEP free-of-charge causes conflicts between the interests of healthcare providers and interests of patients, and, despite policies to provide PEP free-of-charge, many animal bite victims have to pay for it [18]. The chargeable PEP constitutes a serious barrier to prevention of human rabies, especially in low-income FSU republics like Tajikistan. The situation with human rabies in this country is probably the worst among those FSU republics for which information is currently available. In Dushanbe, the capital of Tajikistan, free-of-charge PEP is provided to only 3% of children under 14, while in the rest of the country PEP is administered on a fee-paying basis only. The population in Tajikistan is almost double the population of Georgia, but the rate of human mortality from rabies in 2014 was similar and reached 0.8 per million inhabitants [14]. Access to PEP is particularly difficult for poor people living in remote rural areas of Tajikistan, who are most at risk of rabies and upon whom, the largest burden of rabies falls. For many of them, PEP is neither available nor affordable, while there are also cases when patients start the course of treatment, but then obliged to interrupt it due to financial incapability to meet incurring costs (e.g. transport, accommodation, food etc.).

Barriers to prevention of deaths from human rabies that are currently faced by FSU republics are typical for almost all least developed and developing countries in Eurasia. Considering that recovery from the global financial crisis may take significant time, it is expected that governments of these countries will seek an alternative approach which will allow them to efficiently prevent human deaths from rabies and direct available funds towards elimination of the disease in animals. One of the options could be development and production of vaccines, which is time and labor consuming [19,20]. In countries, where there is no local production of rabies vaccine, the governments and other donors will, probably, subsidize a limited number of doses of rabies vaccine, which will reduce their availability. This situation can be aggravated also by two factors: 1) the lack of rabies immunoglobulin for treatment, and 2) the fact that pharmaceuticals have to be imported, which results in lack of access because of the high price. For example, it has been estimated that a course of PEP in Cambodia costs from 10 to 36 USD and that rabies immunoglobulin costs 20-35 USD per dose, in comparison to which the monthly salary of a Cambodian farmer is only 60-80 USD [16]. Countries which produce immunoglobulin (Serbia, Croatia and Ukraine) on the one hand will probably satisfy local demand and ensure access to PEP, but on the other hand such actions on their own are unlikely to reduce the incidence of human rabies. Alternatively, PEP can be a viable option for reducing the number of human cases of rabies, especially those resulting from unreported exposures (which is often the case for children), and delayed or incomplete administration of PEP [14].

Conclusion and Recommendations

One of the principal conclusions is that PEP of human rabies should be administered free of charge, but in a targeted manner. This will foster access of people to PEP irrespective of their financial abilities and help to secure the emergency stock of rabies vaccine. In the majority of FSU republics, PEP is administered via intramuscular route through either 4-dose Zagreb or 5-dose (Ukraine and Tajikistan use a 6-dose) Essen regimen, which requires considerable expenses. Given limited financial resources allocated by the state for procurement of rabies vaccine in FSU republics and the risk of vaccine shortages occurring in medical centers in the event of an outbreak of human rabies, targeted administration of PEP can be of critical importance. This can be achieved through the method of intra-vitam diagnosis of human rabies, developed by the IPC. This method is based on a combination of skin biopsy and PCR technique, which allows ante-mortem confirmation of rabies in humans [21]. The intra-vitam diagnosis will not only facilitate detection and management of human rabies and prevention of avoidable human deaths from this infection, but will also help to foster transparency of reporting and to raise awareness of governments and societies about the risk of the disease. Clinical trials have demonstrated the high sensitivity (98.3%) of this technique in comparison with other methods of molecular diagnosis of human rabies [22]. This method can be used for ante- and post-mortem diagnosis of human rabies and can be applied not only in countries where post-mortem necropsy is a common practice, but also in countries where it is prohibited for religious reasons.

Though the incidence of human rabies in FSU republics does not justify PrEP of the disease, consideration should be given to this approach from an economical point of view in republics where the number of PEP administered per million inhabitants is high (e.g. Georgia, Kazakhstan and Tajikistan), with the focus on at risk population groups, for example children. The Philippines have introduced PrEP of rabies in schoolchildren in areas where the disease was highly enzootic and the incidence exceeded 2.5 cases per million inhabitants. PrEP does not obviate the need for PEP after an exposure to rabies, but it reduces the number of required vaccine doses and visits (two booster doses provide a rapid and appropriate immune response and eliminate need for use of immunoglobulin). In the case of schoolchildren, PrEP has the advantage of being adapted to intradermal vaccination and, as it can be programmed, vaccine wastage can be avoided [14]. Alternatively, the strategy for the administration of PEP should be revised on the basis of estimation of costs incurred by victims of animal bite. When PEP is provided free-of-charge, the recently developed 1-week intradermal regimen and the Zagreb intramuscular regimen are most advantageous for patients, because they reduce the number of visits. However, both regimens have drawbacks as the 1-weekintradermal regimen is not yet approved by the WHO, while the Zagreb regimen is approved by the WHO, bur requires for more vaccine. The effect and cost efficiency of this approach should be determined and then, if appropriate, put into practice to enable public health authorities to reduce costs for animal bite victims and to prevent shortages of vaccine [18].

Though precise data about the source and incidence of human rabies in most of the FSU republics is still lacking, veterinary and public health specialists converge in opinion that the overwhelming majority of cases are caused by dog bites. Their opinion corresponds to information of the WHO, according to which dogs present the main risk of rabies for humans in Eurasia. In the European part of FSU area, this risk is considered as low (Estonia, Latvia and Lithuania) and moderate (Belarus, Moldova, Ukraine and Russia), while in Caucasian (Azerbaijan, Armenia and Georgia) and Asian (Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan and Uzbekistan) parts it is high [23]. In this situation, PrEP of community dog populations based on "catch-sterilization-release" strategy could be one of the feasible options. It should, however, be noted that the term "community dogs" is not applicable in all countries of Eurasia and therefore this approach cannot be widely applied, or should be implemented taking account the risk that so called "community dogs" are actually stray or feral. Coverage of populations of such dogs by the PrEP using parenteral and oral rabies vaccines is extremely difficult, despite relevant vaccines have been developed and tested in field trials [24]. The restriction of access to feed with the aim of decreasing the reproduction rate in populations of feral and stray dogs can also be effective, but such an approach could be misunderstood and opposed by populations. Besides, it should be preceded by years of public awareness, education programs and strict control over trade in dogs [25].

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