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Why Is There Still Rabies in the World? - An Emerging Microbial and Global Health Threat

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Abstract: This review reports on why is there still rabies in the world?-an emerging microbial and global health threat. Rabies remains an important public health issue in the world. While rabies has been controlled throughout most of the developed world, it remains a significant burden in developing countries, particularly in Africa and Asia. Although industrialized countries have been able to contain recent outbreaks, many resource-limited and transitioning countries have not been able to react adequately. Although, a vaccine-preventable disease, the annual number of human deaths caused by rabies is estimated to be 35,000 per year, mostly in Africa, Asia and Latin America. Though, dogs have been identified as being primarily responsible for the transmission of rabies in human and other domestic animals, known pathogenesis and available data suggest that all or nearly all cases of human rabies attributable to bats were transmitted by bat bites that were minimized or unrecognized by the patients. One of the key for controlling rabies is to focus on the animal reservoir. The high incidence of rabies in some country led to numerous concerns attributed to a potential carrier-dog phenomenon, undocumented transmission of rabies virus from wildlife to dogs, counterfeit vaccines, vaccine mismatching and seroconversion testing in patients after their completion of postexposure prophylaxis. However, the number of reported human rabies cases, particularly in Africa, greatly underestimates the true effects of the disease. Contributing factors include failure to seek treatment at healthcare facilities, failure to make a laboratory diagnosis and failure to report the disease. The disconnection between human and dog rabies in developing world reflects a lack of awareness of the concept of one medicine, or health without regard to species, in approaches to rabies control in the public health system. Another factor contributing to the endemicity of rabies in the world could be attributed to low vaccine coverage. Although there are many factors that contribute to the epidemic or endemic nature of rabies in the world, the single most important factor is the failure to immunize domestic dogs, which transmit rabies to humans. Regional and local disease resurgence occurs, due in part to a combination of political and economic instability, environmental perturbations and shifting government priorities. Indeed rabies is a widely distributed zoonotic disease of major public-health importance and an emerging as well as re-emerging microbial and global health threat but a preventable problem. Surveillance strategies for rabies and other rabies-ralated viruses in the world, particularly Africa must be improved to better understand the epidemiology of this virus and to make informed decisions on future vaccine strategies.

Key words: Containment · Endemicity · Low vaccination coverage · Public health issue · Rabies · Zoonoses

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INTRODUCTION

Rabies is a widely distributed zoonotic disease of major public-health importance [1]. Rabies is one of the most typical zoonosis that has been well known since ancient ages and has been known for more than 4300 years [2]. Rabies remains an important public health issue in the world. It is the most important zoonotic disease in most countries of the world. Rabies, being a major zoonotic disease, significantly impacts global public health [3]. Public concern and fears are most focused on dogs as the source of rabies [4]. Rabies is an enzootic viral disease widespread throughout the world. It is invariably fatal once clinical signs are apparent. The majority of human rabies deaths occur in developing countries. It also kills an estimated 35,000 per year, mostly in Africa, Asia and Latin America [5]. Although it is a vaccine-preventable disease, the annual number of human deaths caused by rabies is estimated to be 32,000 in Asia [6]. India alone reports more than 50% of the global rabies deaths [3]. Rabies is mainly a disease of animals. Rabies virus (RV) is the prototype member of the genus Lyssavirus, which causes acute encephalomyelitis in mammals, including humans, throughout the world. The disease is independently maintained by several species of mammals within the orders Carnivora and Chiroptera [7]. Its occurrence in man and domestic animals is well known but the importance of wild animals in its spread has not been determined. Usually humans contract rabies through rabid animal bite. However, human-to-human transmission of rabies virus also occurred through organ transplantations [2]. Basically, the mode of transmission of rabies include bite from a rabid dog, aerosol contamination of mucous membrane, bruised skin or fresh wound licked by a rabid animal [8]. Dogs are the primary source of infection to humans and other domestic animals. It is also transmitted through vampire bats. Transmammary and transplacental transmission has been reported. However, the global origin of enzootic rabies in dogs and in other terrestrial carnivores remains unknown but likely pre-dates the origin of dogs 15,000-100,000years ago [9]. The known pathogenesis of rabies and available data suggest that all or nearly all cases of human rabies attributable to bats were transmitted by bat bites that were minimized or unrecognized by the patients [8].

Rabies originated about 3000BC from the word rabha meaning violence. It is a viral disease of CNS leading to death of affected animal in most cases. The disease is acute progressive encephalitis characterized by changes in behavior like agitation excitation and drooling of saliva. At first there might not be any symptoms. But weeks, or even years after a bite, rabies can cause pain, fatigue, headaches, fever and irritability. These are followed by seizures, hallucinations and paralysis. Rabies is almost always fatal. Rabies is found all over the world except Australia, Antarctica and some islands where there is strict quarantine system, rigorous eradication or natural barrier like mountains and rivers. According to Turner [10], a number of countries throughout the world have been free from rabies for many years; some are reported to have eliminated the disease and in others it has reappeared after variable periods of time. Apart from these minor variations, however, the global distribution of rabies over the last five to ten years (as at that time) appears unchanged and the disease continues to pose both public health and economic problems of varying severity in all continents except Australia and Antarctica. By 1995 the world estimate was about 70,000 deaths in humans per year worldwide. However, there are only about 35,000 notifications per year [5].

Rabies infection in humans is still a major public health problem all over the world. Though, the epidemiology, virology, transmission, pathology, clinical manifestations, diagnosis and treatment of rabies infection have been described extensively by many authors. Yet the incidence of rabies is increasingly on the high side. Intraspecies RV transmission maintains the disease within geographically discrete areas by distinctive virus variants and lineages, which can be identified either by panels of monoclonal antibodies or by genetic analysis [7]. Interspecies transmission of rabies often results in ecological bottlenecks and epidemiologic dead ends. However, during rabies epizootics or long-term enzootics, novel rabies reservoirs may emerge and produce outbreaks involving closely related RV variants [7, 11].

Historically, substantial technical progress throughout the 20th century led to the development of safe, affordable and efficacious animal and human vaccines, resulting in declining disease burdens in selected developed and developing countries [12]. Clearly, according to Velasco-Villa *et al*. [7], canine rabies elimination is needed on a global level. Vaccination of dogs should be maintained until all dog-related lineages and biotypes currently circulating in wildlife have been eliminated. The canine origin of these viruses makes them prone to return to dogs, where the disease may easily become enzootic again without proper attention related to laboratory-based surveillance, prevention and control. Regional and local disease resurgence occurs, due in part to a combination of political and economic instability, environmental perturbations and shifting government priorities [12]. However, this review therefore reports on why is there still rabies in world?-An emerging microbial and public health threat.

MATERIALS AND METHODS

Rabies is one of the better known encephalitis viruses of the family Rhabdoviridae and genus Lyssavirus. In the sylvatic cycle, this infection is maintained as an enzootic disease in several species, such as foxes, raccoons and bats [13]. Rabies remains a zoonotic viral disease that affects human, domestic and wild animals. Two types of rabies exist, this include sylvatic and urban. It is an acute, highly contagious and fatal disease caused by rabies virus (RABV), a bullet–shaped, enveloped RNA virus 180-75nm with projections and helical nucleocapsid known as Lyssavirus type 1 in the family Rhabdoviride and marked by a long and variable incubation period [8]. The prototype lyssavirus genotype and species, rabies virus (RABV), has a single, continuous, negative-strand RNA of ˜12,000nt that codes for 5 proteins: nucleoprotein, matrix protein, phosphoprotein, glycoprotein and polymerase [14]. It is very sensitive to some environmental factors rapidly destroyed by direct sunlight, U.V. irradiation, heat at 60% for five minutes lipid solvent (70% alcohol and ether), sodium deoxycholate, trypsin and common detergents [8].

RABV is highly neurotropic and functionally conservative. It is transmitted to animals and humans through close contact with saliva from infected animals [8]. It is transmitted mainly through animal bites, although rare nonbite exposure routes have been reported. Because of this characteristic, the dissemination of rabies is relatively slow [15]. It is transmitted to animals and humans through close contact with saliva from infected animals. Once symptoms of the disease develop, rabies is fatal to both animals and humans [8]. The spread of the disease needs a minimum threshold support of host population density. Therefore, the frontline of waves of rabies infections garners little public attention [15].

The Lyssavirus genus was created after isolation of several viruses in Africa and Europe that were related to, but serologically distinct from, RABV [16]. The genus Lyssavirus currently includes rabies virus (RABV) (genotype 1) and 6 rabies-related viruses consisting 6 genotypes (gts) or species: 3 from Africa, Lagos bat virus (LBV) (genotype 2), Mokola virus (MOKV) (genotype 3) and Duvenhage virus (DUVV) (genotype 4) which have been found only in Africa [16]; European bat lyssaviruses 1 and 2 (EBLV1 and 2) (genotypes 5 and 6); and Australian bat lyssavirus (ABLV) (genotype 7) [16, 17] and diversity may expand with the addition of new isolates from Eurasia [18], which are tentative species in the Lyssavirus genus [16]. Other viruses in this genus are: Kotonkan and Obodhiang. Strains of RABV (genotype 1) undergo genetic adaptation to particular animal hosts so that within specific areas the disease is manifested and transmitted predominantly by 1 host species. The canid, or dog, biotype of RABV is the most widely distributed in the world [16, 17]. Some novel lyssaviruses identified in bat species in the former Soviet Union are considered putative genotypes (gts) within this genus [19].

Dog rabies has been recognized since the first human civilizations. However, the possible origins of disease in this species likely pre-date its direct associations with humans. Over time, RVs have had the opportunity to evolve within the context of the human–dog bond and to generate a suite of genetically distinguishable and geographically circumscribed variants and lineages [7]. Dog RVs cause >55,000 human deaths annually, mostly in Asia and Africa. In the Americas, despite a 90% reduction of cases during past decade, the domestic dog still poses the greatest public health hazard with regard to rabies [7]. Also, from literatures, several bat species are reservoir hosts of zoonotic viruses and therefore can be a public health hazard. Lyssaviruses of different genotypes have emerged from bats in America (Genotype 1 rabies virus; RABV), Europe (EBLV) and Australia (ABLV), whereas Nipah virus is the most important recent zoonosis of bat origin in Asia. Furthermore, some insectivorous bat species may be important reservoirs of SARS coronavirus, whereas Ebola virus has been detected in some megachiropteran fruit bats [20]. Thus far, EBLV is the only zoonotic virus that has been detected in bats in Europe and ABLV (gt7) has only been identified in Australia [16]. New zoonotic viruses may emerge from bat reservoirs and known ones may spread to a wider geographical range [20].

Although gt1 viruses have a global distribution, gt5 and gt6 viruses are restricted to Europe and gt7 viruses are limited to Australia. Natural infections with gt2, gt3 and gt4 viruses have been found only in Africa [19]. RABV (genotype 1) has never been isolated from bats outside North and South America, but rabies-related viruses have been isolated from bats elsewhere [17]. Recognized lyssavirus genotypes are divided into 2 serologically, pathogenically and genetically distinct phylogroups [16]. One phylogroup consists of Mokola virus and LBV (group II), while all other genotypes are in group I. Members of phylogroup I are reported to be pathogenic for mice when introduced intramuscularly and intracerebrally. In contrast, members of phylogroup II are believed to be pathogenic in mice only when introduced by the intracerebral (i.c.) route [16]. Commercial vaccine strains belong to gt1 (RABV) phylogroup 1 and these vaccines provide protection against RABV and all the other members of phylogroup I. However, laboratory data

suggest that these vaccines (gt1 based) will not offer protection against lyssaviruses in the phylogroup II cluster [16, 21]. On the basis of criteria proposed for lyssavirus phylogroups, West Caucasian bat virus could be considered an independent phylogroup III because of genetic distance and absence of serologic cross-reactivity with phylogroup I and II viruses [16, 21].

In Africa, LBV and DUVV are associated with bats, but MOKV is uniquely associated with shrews and rodents, not bats. Fifteen isolations of LBV have been reported, including 8 from fruit bats and a cat in KwaZulu-Natal Province of South Africa, but the virus has never been associated with human disease [17]. LBV was first isolated from a fruit bat (Eidolon helvum) in 1956 on Lagos Island in Nigeria [22]. Fourteen isolations of this virus have been reported throughout Africa, including 8 in South Africa [16, 23]. Most LBV isolates were obtained from bats; 2 were from domestic cats and 1 was from a domestic dog in Ethiopia. LBV has never been isolated from any terrestrial wildlife species. Although cases in domestic animals have been recorded, no human cases of infection with LBV have been documented and although the incidence of the rabies-related viruses seems to be low, human exposure to these viruses is possible [16].

MOKV has been isolated from shrews, rodents, cats and a do in Africa and from 7 cats with rabies-like disease in KwaZulu-Natal and Eastern Cape provinces of South Africa [17]. The virus is believed to have caused rabieslike disease in 2 persons in Nigeria in 1969 and 1971, shortly after its initial discovery in shrews in 1968, but no cases of human infection have subsequently been recognized [24]. DUVV was discovered in 1970 when it caused fatal rabieslike disease in a person bitten by an unidentified insectivorous bat ˜150 km northwest of Johannesburg, South Africa [17]. In 1981, the virus was isolated from what is believed to have been a Miniopterus schreibersi insectivorous bat caught in daylight by a cat in Makhado town in Limpopo Province, South Africa and in 1986 the virus was recovered from an insectivorous bat, Nycteris thebaica, trapped in a survey in Zimbabwe [17]. With the exception of MOKV, all lyssavirus gts and putative gts have been isolated exclusively or most frequently from chiropteran species. MOKV has never been isolated from these species, but only from terrestrial mammals [19]. The first MOKV was isolated from shrews (Crocidura sp.) in Nigeria in 1968. Since then, $\geq$20 isolates of this lyssavirus have been found throughout Africa (Cameroon, Central African Republic, Ethiopia, South Africa and Zimbabwe) [19, 22, 24].

In a study by Salmün-Mulanovich *et al*. [13], bats from the genus Carollia were collected. Seventeen bats were antibody positive to rabies virus, for an antibody prevalence of 10.3% [13]. Haematophagous bats, including D. rotundus, are usually the species associated with sylvatic bat rabies outbreaks in South America, but little is known about the role of nonhematophagous bats. An investigation in Chile found that nonvampire bats may in fact serve as adequate vectors of sylvatic rabies and even confirmed a single human infection of nonvampire-bat variant rabies linked to a nonhematophagous bat. Likewise, PAHO reported 3 cases of sylvatic rabies transmitted by nonhematophagous bats in 2004 [25]. This may suggest that insectivorous and frugivorous bats have a more specific role in the transmission of rabies virus in South America [13].

In theory, all mammals are susceptible to RABV infection [15]. In China, dogs play the dominant role in rabies transmission [26]. Statistically, >95% of human rabies cases in China are due to rabid dog bites [27]. In isolated serologic studies of rabies in wildlife such as badgers, raccoon dogs, rodents and bats, no RABV was successfully isolated from these animals. Rodents do not serve as reservoirs for rabies [15]. However, all RABV isolates characterized by phylogeny using the N and G gene sequences are categorized into classic RABV genotype 1 [28]. In addition, RABV isolates from dogs on all continents are grouped into genotype 1. Phylogeny analyses reinforce the perspective that vaccine matching in most country is redundant. In a rabies-epidemic region such as China and Nigeria rabies in wildlife may result from spillover from dogs. Without proper investigation of animal population density and characterization of the RABV isolates wildlife rabies in any country can be elucidated only after dog rabies is well controlled [15]. Host identity is rarely a problem in domestic animals, but wildlife species show potential uncertainty, such as demonstrated in the case reported by Markotter *et al.* [16]. One important aspect of disease epidemiology is accurate information about the host species involved, which enables informed decisions to be made with regard to the epidemiologic patterns and potential threats to public and veterinary health [16]. However, urban (dog-mediated) rabies has almost been completely eradicated, except from cases from failed vaccination, increased mortality due to hunting and rabies, dogs and foxes and along their dispersal routes to maximize the effect of vaccination [29].

Control, Elimination and Possible Eradication of Rabies in the World: How Far Have We Gone?: The term "emerging diseases" has been used recently to refer to different scenarios, all of which indicate changes in the dynamics of disease in the population [30]. Eradication is defined as reduction of the worldwide incidence of a disease to zero as a result of deliberate efforts, obviating

the necessity for further control measures [31]. Eradication is the permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts; intervention measures are no longer needed. Eradication represents the ultimate in sustainability and social justice [32]. Between the extremes of disease "control" (reduction in incidence and/or prevalence) and "eradication," several intermediate levels of impact on diseases may be described. The term "elimination" is sometimes used synonymously with "eradication," but it refers to a single country, continent, or other limited geographic area, rather than global eradication. True eradication usually entails eliminating the microorganism itself or removing it completely from nature, as in the case of smallpox virus, which now exists only in storage in two laboratories [31]. It is also theoretically possible to "eliminate" a disease in humans while the microbe remains at large, as in the case of neonatal tetanus, for which the WHO in 1989 declared a goal of global elimination by 1995.

Finally, "elimination" can be defined as control of the manifestations of a disease so that the disease is no longer considered "a public health problem," as an arbitrarily defined qualitative or quantitative level of disease control (e.g., WHO's goal of eliminating leprosy by the year 2000, which is defined as reducing its incidence to a level below one case per 10,000 population) [31]. The term control means to restrain or limit infection, e.g. in expression, occurrence, or rate of increase. Control of animal-borne diseases is a major challenge faced by applied ecologists and public health managers. To improve cost-effectiveness, the effort required to control such pathogens needs to be predicted as accurately as possible [29]. While canine rabies has been controlled throughout most of the developed world, it remains a significant burden in developing countries, particularly in Africa and Asia [1].

European Countries: The population of Western Europe includes ˜20 million persons living in nonnative countries; most are settled immigrants. One third were born in a country outside of Europe [33]. Rabies due to two independent and different genotypes of lyssaviruses - EBLV type 1 and type 2 - is present in many European countries. The disease is fatal in humans and has been described in Europe following a bat bite [34]. Infection is usually seen in bats, the primary reservoirs of the viruses but a few spillover infections have been seen in three other species: stone martens, sheep and humans. According to Stantic-Pavlinic [34], spillover infections (with the exception of the two human cases) were EBLV-1 only. No EBLV-2 spillover cases have been reported in terrestrial animals. According to Harris *et al*. [35], in a study on passive surveillance for eblvs in the UK, the proportions and numbers of each species of bats submitted from different regions varied considerably, partly owing to inherent biases in the passive surveillance and there were seasonal variations in the numbers, sex and age of the bats. Contact with cats was reported in approximately 30 per cent of the bats submitted. Daubenton's bat (*Myotis daubentonii*) was the only species found to be positive for lyssavirus infection, with four cases of eblv type 2 identified, in 1996, 2002, 2003 and 2004. No active infection with eblv type 1 was recorded in their [35] study. However, red fox also remains the main reservoir of rabies in Poland [36]. In France, illegal importation of animals still poses a risk of rabies in a native French animal and person-to-person transmission has only been observed as a result of grafts (cornea) transplant [37].

North Rhine Westphalia had to face the problem of rabies in suburban and urban areas of the Ruhr, one of the most densely populated areas in Europe, during the final phase of rabies eradication. Here, rabies has been endemic in a very limited area in the southernmost parts of the federal state, reflecting similar topographical and geographical features of a fragmented landscape [38]. Whereas the rabies incidence in North Rhine Westphalia was unaltered, the increase in rabies incidence was due mainly to a deterioration of the rabies situation in the border area of Bavaria and Hesse due to due to inconsistent hand baiting [38].

American Countries: Methods for antigenic and genetic identification of rabies samples isolated in the Americas have contributed effectively to the development of health programs, as well as recognition of possible wild reservoirs of urban rabies. The emergence of new cycles in Latin American wildlife indicates the need to strengthen surveillance programs in wildlife species and research development for the evaluation of the feasibility of oral vaccination interventions [39]. Rabies infections acquired by humans from wild animals, or sylvatic rabies, now represents the primary source for human infection in some region [40], with a similar trend for Peru [41]. Rabies has also continued in some American countries due to spilloverr as in the case of arctic fox (Alopex lagopus)–variant rabies that had spilled into (i.e., had been transmitted to another species) red foxes [42]. Additionally, the lack of surveillance for bat populations in the in Latin America areas prevents further inference about a possible source of infection among these bat populations [13].

In the United States, rabies remains enzootic among bats and several species of terrestrial wildlife due to spillover transmission of wildlife rabies to domestic animals and has therefore remains a public health threat [43]. Though, oral rabies vaccination programs have been implemented to control the spread of wildlife rabies, yet the current surveillance systems are inadequate for the efficient management and evaluation of these large scale vaccine baiting programs [44]. Progress has been made in preventing the spread of raccoon rabies from the eastern United States. Nevertheless, the most profound challenge facing the program is the need for baits and oral vaccines with improved effectiveness in other mesocarnivore reservoir species, such as skunks and mongoose [45]. Chile is undergoing an important degradation of many wild-life biotopes, affecting their diversity and contributing to the dissemination of zoonoses. The intensification and accelerations of the anthropogenic deterioration of the biosphere in Chile, as results of the unrestricted utilization of natural resources and global climate change, suggests that emergence of new zoonoses in the near future will lead to important public health and economic problems [46]. The need to vaccinate annually is dictated mainly by high death rates for juveniles and a relatively young age structure for raccoons in North America; juveniles often account for 50% of raccoon populations [42].

Asian Countries: Rabies is a serious problem in the 11 states that make up Central Asia [47]. A steady increase has been reported over the past 10 years with more than 3,200 cases reported in 2006. Although there are many factors that contribute to the epidemic or endemic nature of rabies in these countries, the single most important factor is the failure to immunize domestic dogs, which transmit rabies to humans [48]. Killing dogs and cats not only removes a major check on the growth of the rat and mouse population, for instance, but invites in more problematic species to take their places. Many Asian cities now have hard-to-control populations of feral pigs, macaques and even jackals, leopards and cobras in their suburbs, in consequence of rapidly reducing dog populations through sterilization in the more enlightened communities and elsewhere through the combined effects of extermination and great increases in motor vehicle traffic [49].

The high incidence of rabies in China leads to numerous concerns attributed to a potential carrier-dog phenomenon, undocumented transmission of rabies virus from wildlife to dogs, counterfeit vaccines, vaccine mismatching and seroconversion testing in patients after their completion of postexposure prophylaxis. The disconnection between human and dog rabies in China reflects a lack of awareness of the concept of one medicine, or health without regard to species, in approaches to rabies control in the public health system [15]. Reemerging rabies in China has led to a carrier-dog myth, strict pet population control policies, counterfeit vaccines (low antigen, generating <0.5 IU of virus-neutralizing antibodies after administration), vaccine matching, seroconversion testing with an ELISA after completion of postexposure prophylaxis (PEP) in humans, virus-neutralizing antibody titration in vaccinated animals because of inferior vaccines and other related issues [15]. Rabies following dog bites is the number-one cause of death from infectious diseases in China, in part because of absent or incomplete PEP for poor rural residents. Thus, the complete absence of reported dog-associated rabies is unusual [50].

Another factor contributing to the endemicity of rabies in in Far East Asia could be attributed to low vaccine coverage. According to Fu [48], dog vaccination is at or below 5% in many of these countries and cannot stop the transmission of rabies from dogs to dogs, thus to humans. In India, there is little data available on the actual risk to travelers of being possibly exposed to rabies. This data would be useful in advising travelers who are considering rabies pre-exposure immunization. In addition, it is not known how many travelers are already pre-immunized when they are bitten by a possibly rabid animal. Increased knowledge of the complexity of the rabies situation in India should spur efforts to improve public awareness and to better control this disease [51].

In Japan, no rabies case has been reported for about 50 years. However, in November 2006, two cases of human rabies infections were reported in the country. These patients were bitten by dogs during travel in the Philippines and did not receive pre- and post-exposure prophylaxes. With the mounting numbers of Japanese travelers every year, the risk of infection increases especially to those who visit regions where the disease is endemic [52]. With rabies being epizootic in many Asian countries, where more than 50% of the rabies deaths in the world occur. The Japanese travelers who visit these countries every year may not be aware of this fact since no rabies occurs in their own country. Therefore, the risk of being bitten by a rabid animal abroad and developing rabies after returning to Japan seems to be high [2].

African Countries: Although industrialized countries have been able to contain recent outbreaks of zoonotic diseases, many resource-limited and transitioning countries have not been able to react adequately. The key for controlling zoonoses such as rabies, echinococcosis

and brucellosis is to focus on the animal reservoir [53]. However, the number of reported human rabies cases, particularly in Africa, greatly underestimates the true effects of the disease. Contributing factors include failure to seek treatment at healthcare facilities, failure to make a laboratory diagnosis and failure to report the disease [54]. Dog rabies control relies principally on the mass immunization of dogs in order to achieve population immunity levels sufficient to inhibit rabies transmission [55]. In Africa, such high levels of population immunity are rarely achieved due to a number of reasons. Oral immunization has been shown to be an effective means of inducing high levels of immunity in fox populations in several European countries and this technique has been mooted as a means of overcoming the logistical problems of delivering injectable rabies vaccines to dogs [55]. Although highly effective if administered correctly, PEP is much more costly than vaccination of domestic dogs [54].

Cross-sectoral assessments of interventions such as mass vaccination for brucellosis in Mongolia or vaccination of dogs for rabies in Chad consider human and animal health sectors from a societal economic perspective [53]. Unfortunately, dog vaccination is difficult in many developing countries because of high dog turnover rates, shortages of funding and personnel and competing priorities [54]. Combining the total societal benefits, the intervention in the animal sector saves money and provides the economic argument, which opens new approaches for the control of zoonoses in resource-limited countries through contributions from multiple sectors [53].

The origin of mongoose rabies in South Africa is not clear. Epidemiologic cycles among yellow mongooses and other Herpestidiae are well established and shown to be impossible to extinguish or control by the attempted eradication or control of vector and host density [16]. Mongoose rabies may have originated from a spillover event of a bat lyssavirus progenitor in an event similar to the spillover described by Markotter *et al*. [16]. Cohen *et al*. [54] described an outbreak of human rabies in a province of South Africa where rabies had been well controlled for >10 years. Late recognition of this outbreak resulted in delayed implementation of control measures. Although the clinical features of classic rabies have been described as unmistakable, the diagnosis may be missed due to low index of suspicion and variable clinical features, as occurred in the outbreak reported by Cohen *et al.* [54].

Poisoning street dogs had already been introduced as long as 2,000 years earlier in Egypt-and poisoning campaigns that caused dog populations to briefly crash might have contributed to the conditions that drew African desert cats into Egyptian cities to hunt rats and mice. According to Clifton [49], those cats became the progenitors of today's domestic house cats and feral cats. In Malawi several hundred to several thousand people are treated annually with purified chick embryo vaccine. However, in many areas the vaccine is not available and it was not given to any of our patients, even though several did seek treatment after a dog bite [56]. In Nigeria where dog bites continue to be the main mode of transmission of the disease to man, it remains a serious public health hazard [8].

Factors Contributing to Difficulty in the Eradication of Rabies in the World: The development of the first rabies vaccine by Pasteur surely had been hoped to eliminate or at least drastically reduce its incidence [57]. However, this goal has not been completely achieved because rabies is maintained in many animal reservoirs, including both domestic and wild. There are still many aspects of the pathogenicity of rabies that are unknown. For example, we have no explanation for the long incubation period (up to 6 years). Furthermore, new patterns of rabies infection present a problem for epidemiologists and virologists alike. There are several cases of human rabies in which there was no history of a bite [57].

Rabies in humans can be prevented by appropriate postexposure prophylaxis and through vaccination of the animal vector, which is not, however, always available and affordable in resource-limited countries [53]. Risk factors for rabies including; risk behaviors, associated conditions, protective factors and unrelated factors. However, eradication of rabies from the wildlife would prove to be extremely difficult. Transmission would confer extra difficulty in terms of eradication. Whether a virus disease can be eradicated or not depends on many factors. Factors that can increase your risk of rabies include: Traveling or living in developing countries where rabies is more common, including countries in Africa [52]. Other factors such as the size and intensity of infectious foci, the rapidity of spread, difficulty of eradication, etc., will influence these risk factors. In order to prevent the transmission of rabies in a dog population, it is theoretically necessary to vaccinate a minimum of 60 to 70% of the dogs. Even countries with potentially sufficient resources, however, do not often meet and sustain these rates. One reason for such failure might be that individual dog owners might feel that it is too expensive to vaccinate their pets [58].

Increased Human Activities: Rabies can emerge either through introduction into a new population or when the

interaction with the vector changes; emergence is also influenced by microbiological adaptation and change, global travel patterns, domestic and wild animal contact and other variants in human ecology and behaviour [59]. Although the discovery of such zoonoses is often related to better diagnostic tools, the leading causes of their emergence are human behavior and modifications to natural habitats (expansion of human populations and their encroachment on wildlife habitat), changes in agricultural practices and globalization of trade. However, other factors include wildlife trade and translocation, live animal and bushmeat markets, consumption of exotic foods, development of ecotourism, access to petting zoos and ownership of exotic pets [60]. Among these causal factors affecting rabies eradication are the burgeoning human population, the increased frequency and speed of local and international travel, the increase in human-assisted movement of animals and animal products, changing agricultural practices that favour the transfer of pathogens between wild and domestic animals and a range of environmental changes that alter the distribution of wild hosts and vectors and thus facilitate the transmission of infectious agents [61]. In effect, mechanization of transport and improvements in urban sanitation reallocated the carrying capacity of the human environment. Instead of supporting dogs and cats who lived directly off of refuse and rodents, the human environment evolved to support dogs and cats who lived on refuse that was processed into pet food, fed to them in human homes. This same reallocation of carrying capacity has occurred in Western Europe and is occurring now in Eastern Europe, India, China, Ethiopia and wherever else economic development is transforming former hubs of agrarian commerce into technologically developed modern cities [49].

Rabies is a fatal disease and increased international travel is one of the important factors affecting eradication of rabies globally [62]. Human activities may also be a source of wildlife infection, which could create new reservoirs of human pathogens [60]. Globalization is also leading to a rise in the emergence of diseases. The emergence of these pathogens as significant health issues is associated with a range of causal factors, most of them linked to the sharp and exponential rise of global human activity [61]. Deforestation, development of human habitat and mining activities has been suggested as risk factors associated with the reemergence of vampire bat rabies in humans in the Amazon Basin [60]. The emergence of rabies and its expansion has been directly linked to development of agricultural activities [60]. However, reemergence of zoonotic diseases that had been controlled from their domestic animal reservoirs is also of major concern. The geographic nature of these rabies foci or groups suggests that dogs are not moving, per se, but that human-related activities may account for these phenomena. Spread of RABVs from high-incidence regions, particularly by the long-distance migration or transprovincial movement of dogs caused by human-related activities, may be one of the causes of recent massive human rabies epidemics [63]. However, the world is experiencing an increase in emergent infections as a result of anthropogenic changes of the biosphere and globalization [46]. Global warming and unrestricted exploitation of natural resources such as forests and fisheries, urbanization, human migration and industrialization of animal husbandry cause environmental destruction and fragmentation. These changes of the biosphere favor local emergence of zoonoses from their natural biotopes and their interaction with domestic animals and human populations, favor the dissemination of these zoonotic pathogens worldwide [46].

The globalization of food (and feed) trade, facilitated by the liberalization of world trade, while offering many benefits and opportunities, also represents new risks [64]. Worldwide movement of animals has increased the potential for the translocation of zoonotic diseases, which pose serious risks to human and animal health [65, 66]. The magnitude of the global movement of animals is staggering. However, recent data suggest that civets may be only amplifiers of a natural cycle involving trade and consumption of bats [60]. Most emerging infectious diseases are zoonotic; wildlife constitutes a large and often unknown reservoir. Wildlife can also be a source for reemergence of previously controlled zoonoses. Although the discovery of such zoonoses is often related to better diagnostic tools, the leading causes of their emergence are human behavior and modifications to natural habitats (expansion of human populations and their encroachment on wildlife habitat), changes in agricultural practices and globalization of trade [60].

Other factor affecting eradication of rabies includes consumption of exotic foods, development of ecotourism, access to petting zoos and ownership of exotic pets. Furthermore, our quest for close contact with exotic pets puts us at risk for exposure to zoonoses. Industrialized nations' new taste for exotic food has also been linked with various zoonotic pathogens or parasites [60]. For instance, wildlife tourism is among the top exporting activities of Tanzania and Kenya and generates an annual income of approximately half a billion US dollars. Adventure travel is the largest growing segment of the leisure travel industry; growth rate has been 10% per year since 1985. This type of travel increases the risk that tourists participating in activities such as safaris, tours,

adventure sports and extreme travel will contact pathogens uncommon in industrialized countries [60]. Petting zoos, where children are allowed to approach and feed captive wildlife and domestic animals, have been linked to several zoonotic outbreaks, including infections caused by rabies [67]. More than 25 outbreaks of human infectious diseases associated with visitors to animal exhibits were identified during 1990–2000. Exposure to captive wild animals at circuses or zoos can also be a source of zoonotic infection. Exotic pets are also a source of several human infections that vary from severe monkeypox related to pet prairie dogs or lyssaviruses in pet bats to less severe but more common ringworm infections acquired from African pygmy hedgehogs or chinchillas [60]. Global migration, social factors and trading activities continue to promote and enhance long-distance movements of rabies-infected animals, increasing the potential risk of reintroducing the disease to regions where the problem has been eliminated. This trend poses new challenges for the regulation of animal movements to attain sustainable elimination [7].

Increasing Population: As in a classic situation, outbreak of rabies in humans followed an outbreak in domestic dogs of the Africa region. Increasing numbers of human rabies cases in Africa have been attributed to increasing numbers in animals [54]. Descriptive epidemiologic analysis showed that the increase in domestic dog populations has contributed to rabies epidemics in the 3 provinces in southern China [68]. Also, outbreak of rabies in humans followed an outbreak in domestic dogs. Increasing numbers of human rabies cases in Africa have been attributed to the mobility of human and animal populations [54]. Other human-related activities, such as persons migrating with their dogs may also contribute to long-distance spread of rabies. While the majority of reported potential rabies exposures are associated with dog and cat incidents in most places, most rabies exposures have been derived from rabid wildlife [43].

Can the high population density of reservoir hosts be reduced? In principal, reducing the density of reservoir hosts could lead to lower transmission rates and prevent disease from persisting in the population. The practical possibilities of doing this depend upon a number of factors. If the reservoir host was a wildlife species, controlling population size would rarely be possible. For domestic dogs, the possibilities would depend upon local peoples' requirement for those dogs [69]. Can contact between wild dogs and domestic dogs be minimized? According to Ginsberg and Woodroffe [69], this would depend upon local peoples' need for domestic dogs. Subsequently, international commerce, human and animal migration and travel, favor the dissemination of these zoonotic pathogens worldwide [46]. However, the animal population itself does not pose a rabies threat. More research is needed to determine whether domestic dogs' movements could be restricted by, for example, requiring that owned dogs be collared, that dogs be tied up at night and shooting unaccompanied dogs [15].

Poor Surveillance and Lack of Public Awareness: Lack of risk communication is one of the factors affecting amd making eradication in the world very difficulty. Many countries, especially those with resource constraints and those in sub-Saharan Africa, lack information on the distribution of zoonotic diseases [54]. Lack of public education campaigns in the developing world [49] is another factor affecting rabies eradication. Though, public awareness of the human health risks of zoonotic infections has grown in recent years [70], reliable data on rabies are scarce in many areas of the globe, making it difficult to assess its full impact on human and animal health [8]. Poor surveillance of rabies-related viruses and poor diagnostic capability in most of Africa are large contributors to our lack of information and the obscurity of the African lyssaviruses [16]. The lack of surveillance data on emerging zoonoses from many developing countries means that the burden of human, livestock and wildlife disease is underestimated and opportunities for control interventions thereby limited [71]. However, laboratories in the developing nations continue to be sadly behind the times in terms of equipment and skills for diagnosing the emerging pathogens [72]. In resource-limited and transitioning countries, many zoonoses are not controlled effectively because adequate policies and funding are lacking [53]. Deficiencies in national veterinary services have contributed to failures in early detection and response; in many regions investigation and diagnosis services have deteriorated [30]. Free-roaming and unvaccinated dog populations may increase the likelihood of transprovincial spread of RABVs. Quick, decisive action to detect and control novel pathogens and thereby contain outbreaks and prevent further transmission, is frequently hampered by incomplete or inadequate data about a new or re-emerging pathogen [59]. Also, policymakers in the developing world often seek for their cities the superficially animal-free appearance of a “modern” city that they see in Europe and the U.S., equating this with ridding themselves of rabies. But casual outdoor observation of European and U.S. cities by daylight is deeply deceptive. European and American cities support even more dogs, cats and wild

animals per thousand humans than the cities of the developing world. They have merely achieved a transition from hosting outdoor animals, seen in daytime, to hosting mostly indoor pets and nocturnal wildlife [49].

Low vaccination coverage and other contributing factors The single most important factor affecting eradication of rabies is the low vaccination coverage in domestic dogs, which transmit rabies to humans [48]. The local increase in the number of rabies cases and the resulting spread of rabies in recent years has also been attributed to inconsistent vaccination, e.g. missing complementary distribution of baits per hand in non-flying zones [38]. Descriptive epidemiologic analysis has also shown that low vaccination coverage has contributed to rabies epidemics [68]. Significantly, less than ideal cross-reactivity with modern biologicals used for veterinary and public health interventions is a major cause for concern among these emerging viral agents [Duvenhage and Lagos bat viruses] [73]. Although rabies is preventable, the high cost of postexposure prophylaxis, compounded by the lack of education and awareness about rabies, limits use of postexposure prophylaxis in many developing countries [51]. Vaccine shortages can result from higher-than-expected demand, interruptions in production/supply, or a lack of resources to purchase vaccines [74]. Each of these factors has played a role in vaccine shortages especially in the United States during the past 20 years. In developing countries, the major cause of vaccine shortages is lack of resources to purchase them [74]. The inferior quality of the domestically manufactured dog vaccine in China has been documented [75]. According to Wu *et al*. [15], vaccine quality control and mass production, rather than matching, are urgently needed and most important for addressing the current rabies problem in China. Any potent rabies vaccine will protect against rabies.

However, the most likely cause of the vaccine failures lies in the vaccination protocols used. Each wild dog was given only a single dose of vaccine. Suzuki *et al.* [4] reported unsatisfactory titre level in their study in comparison with the results from other field investigations with inactivated tissue culture vaccines. Subsidized post-exposure vaccination is the standard response to rabies in India, China and much of Africa. Post-exposure vaccination saves thousands of lives annually, despite many failures when dog bite victims fail to seek treatment soon enough, do not complete the full course of injections, or receive fake, expired, or obsolescent vaccines, a problem particularly prevalent in parts of India and China, where post-exposure vaccines are often made by local suppliers, using formulas elsewhere long abandoned [49]. The paper by Ajayi *et al.* [76] also indicates a disturbing possibility of transmission of rabies by apparently healthy (free of overt rabies signs) stray dogs. Other authors have suggested that this trend may be caused by a carrier state in healthy dogs that remains undetected [77]. If their observations are confirmed, this, in their words, "signifies a new dimension in the epidemiology of the disease in this environment where the high-risk practices are prevalent [78]."

What Next?: So far, several corrective actions taken in most countries in 2005 have resulted in halting rabies spread in the respective areas. Recent epidemiological analysis showed that rabies incidence has significantly decreased and attainment of rabies elimination can be expected in due course. Nevertheless, the implemented vaccination strategy must be continued for more years after the last confirmed rabies case in order to achieve the rabies-free status [38]. Other corrective actions are recommended concerning mainly the weak points that have been identified in developing countries and the preventing measures:

Rethinking: Rabies as a zoonotic disease is among the most important animal and public health problems that affect the well-being of societies worldwide, yet they are too often forgotten or neglected. Because most zoonoses go unrecorded, they call for a rethinking of research and control efforts and the economic consequences. The example of brucellosis demonstrated that interventions in livestock against zoonoses, which would never be cost-effective when uniquely assessed from a public health sector point of view, may become cost-saving when considered from a societal perspective [53]. However, a radical rethink of the vaccination programme is necessary - immunization programmes need not be abandoned, but reassessed. Owing to the effectiveness of local rabies control in industrialized countries, the lack of familiarity with rabies may place certain travelers to countries with a higher prevalence of rabies at higher risk for potential contact with rabid animals, requiring rabies postexposure prophylaxis [1]. Where necessary, some travelers may need to consider rabies pre-exposure vaccination, depending on planned activities and duration of travel within a given country. Travelers to countries where rabies is prevalent should balance the cost and inconvenience of immunization to the benefits of rabies pre-exposure vaccination [1].

Financing: Zoonosis control in general should thus be seen from a global perspective and lead to a call for a

global subsidiary approach for control. International bodies like the World Organization for Animal Health, the Food and Agriculture Organization and World Health Organization should foster establishment of global standards for zoonosis surveillance and control [53]. Fostering of global standards is also part of the WHO International Health Regulations that came into force in mid-2007 and required all countries to do a better job of surveillance for diseases that can spread between countries (www.who.int/gb/edwha/pdf_files/WHA58-REC1/english/Resolutions.pdf). However, these efforts should lead to a global fund for the control of zoonoses or become a component of an extended Global Fund to fight AIDS, tuberculosis and malaria [53].

Substantial evidence documented that the combined effects of human disease caused by zoonoses, as part of the neglected infectious diseases, are in the same range as the classical diseases of poverty such as HIV/AIDS, tuberculosis and malaria [79]. Zoonoses such as rabies should also be included in current global programs and initiatives. Recognition of these facts should result in affected countries applying for funds from the Global Fund to fight zoonotic diseases, AIDS, tuberculosis and malaria. One country not able to carry out early detection and rapid response to animal disease outbreaks can represent a threat to all the others. To approach these threats, new partnerships (e.g., between resource-limited and industrial countries, public and private sectors and animal and public health) and permanent dialogue are needed [53]. It is evident that the interest of the rich countries is to support the others in order to protect themselves [53]. Creating a new global finance facility for the control of zoonoses, similar to or linked with the Global Fund to Fight AIDS, Tuberculosis and Malaria, is timely, is of global interest and represents a further contribution to successful attainment of the Millennium Development Goals [53], but zoonoses such as rabies should also not be neglected. Such a joint facility would allow coherent and integrated control approaches, particularly in the countries with the most serious resources constraints, which in turn would benefit the whole world.

Communication and Reporting: Risk communication is increasingly becoming important in public health. Risk communication offers a two-way communication process that presents the expert opinions based on scientific facts to the public and acknowledges the fears and concerns of the public, seeking to rectify knowledge gaps that foster misrepresentation of risk [80]. Provision of all means of communication to the Virology and Veterinary Services in most developing countries of the world, as it has been noticed that some of them had no internet facilities, the GSM, telephone or fax or any other mean of communication. The radio sets once they used are all out of order and necessitate repair and maintenance. Reporting is tightly linked with the communication. It is highly recommended that the field operators (virologist, biologist, zoologist, parasitologist, veterinarians and animal health technologists/superintendents) should report periodically the zoo-sanitary events they notice and every time they feel that something abnormal is happening. Special instructions should be directed to the State Health and Veterinary Services on that matter. According to the Federal Services, the health officers and veterinarians report monthly to the State Directorate and the Federal Offices report on quarterly basis to the Federal Services; the field technologists report if necessary and the dog owners never report. The dog owners and hunters should be approached by the field veterinary staff in order to obtain their commitment in the diseases control, so they can inform them in case of abnormality.

Knowledge of the association of specific variants with animal hosts has led to increasingly effective control measures that target the hosts responsible for spreading this disease. According to Chomel *et al*. [60], major tasks that should be taken by the international community include better integration and coordination of national surveillance systems in industrialized and developing countries; improved reporting systems and international sharing of information; active surveillance at the interface of rural populations and wildlife habitats, especially where poverty and low income increase risks for pathogen transmission; training of professionals, such as veterinarians, virologists and biologists, in wildlife health management; and establishment of collaborative multidisciplinary teams ready to intervene when outbreaks occur.

Information: Key measures for reducing the dispersion of emerging zoonoses such as rabies include sustainable agricultural development, proper education of tourists about the risks of outdoor activities and better control of the live animal trade (exotic pets, wet markets, bushmeat). Public health services and clinical practitioners (physicians, veterinarians) need to more actively educate the public about the risks of owning exotic pets and adopting wild animals [60]. According to the Veterinary Services, the information has been spread to the veterinary staff and to the administrative responsible but none of the public nor the other agents of the Ministry of Agriculture and Natural Resources or the animal owners

had been informed. It is recommended to perform a public information campaign through the media, in English and local languages, taking care of the content of the messages directed to the Public, avoiding misunderstanding and possible panic. Papers, leaflets or booklets on rabies epidemiology, pathogenesis and control should be prepared and distributed to the veterinary staff and training sessions on clinical and post mortem recognition should be organized. Less elaborated leaflets and posters should be printed for distribution to the villagers, dog breeders and hunters and to other concerned people and displayed in public places.

Awareness: Transmission of rabies to humans can already be greatly reduced by health information and behavior. Interventions in human and livestock should always be accompanied by mass information, education and communication programs. There must be a greater public health effort to educate clinicians and the public about proper response to bat exposures, particularly undetectable bite exposures. Had public health authorities been contacted to collect and test the captured bat for rabies, there would have been no ambiguity as to the appropriate course of action [81]. The awareness of dog owners and hunters should be raised, holding village level meetings. Civil administrative authorities should also be put in state of alert by periodical epidemiological information. An early warning system should be implemented in every State and at the Federal level. Also, to reduce risk for emerging zoonoses, the public should be educated about the risks associated with wildlife, bushmeat and exotic pet trades; and proper surveillance systems should be implemented [60]. Education regarding behavior around unfamiliar animals and general familiarity with local rabies epidemiology is often sufficient to reduce a person's risk of exposure [1].

Investigation: Rabies antibody titration can afford a strong additional guarantee to the vaccination certificates accompanying domestic carnivores during transportation between countries. Quarantine rules should also be adapted to the epidemiological features in the exporting country, e.g. statistics of vaccination failure in cats and dogs and host-virus adaptation of the rabies strains circulating in these countries. Surveillance, early warning and disease emergency preparedness will need to be pursued more vigorously in Africa and the Middle East as vital components of national veterinary services [30]. It is recommended that epidemiological investigation should be carried out by the field veterinary staff and extension personnel, in the villages, asking a single question: "have you noticed any abnormality on dog population?". As suggested by Kuiken *et al.* [82], it is time to form "a joint expert working group to design and implement a global animal surveillance system for zoonotic pathogens that gives early warning of pathogen emergence, is closely integrated to public health surveillance and provides opportunities to control such pathogens before they can affect human health, food supply, economics or biodiversity [60]." In the context of international trade, the choice of the vaccine and the timing of blood tests are critical factors in achieving successful serological test results after rabies vaccination [83].

Preventing Measures: Traditional prevention methods such as vaccinating pets, avoiding wildlife and verifying an animal's rabies status must be continued to reduce costly postexposure treatments (PET). When post-exposure prophylaxis should be continued after return from travel, it is important to know the sort of rabies vaccine injected abroad, because brain-tissue vaccines are less effective in inducing antibody than tissue-culture vaccines [2]. To reduce rabid animals, exposures and costs, oral vaccination of wildlife should also be considered [84]. Current pre-travel interventions are missing certain risk groups entirely and failing to have the desired educational impact in others [85]. The decision whether or not to administer rabies pre-exposure prophylaxis (PEP) to travelers visiting endemic areas is a complex one. Paramount for making that decision is knowledge of the risk of animal bites during travel [86]. If pre-exposure prophylaxis for rabies is given, RIG is unnecessary even after severe exposure. It is thus important to give pre-exposure prophylaxis for rabies to people who plan to go to rabies-endemic areas [87]. Human PEP should be initiated on the basis of diagnosis of biting animals. Reliable national systemic surveillance of rabies-related human deaths and of animal rabies prevalence is urgently needed [15]. A laboratory diagnosis–based epidemiologic surveillance system can provide substantial information about disease transmission and effective prevention strategies [15].

CONCLUDING REMARKS

Rabies could be gone in a decade and could be wiped out across the world, if sufficient vaccinations are carried out on domestic dogs [49, 88]. The continuing structural adjustment program for national veterinary services across the world will need to take into account their transformation from providers of services (e.g., vaccinations, medicines) to inspection and quality

assurance services [30]. While international collaboration exists in dealing with disease emergency situations, there is a need to develop regional and international contingency plans that can be launched as soon as an emergency situation arises. This will only be possible if there is the political will to tackle problems wherever they occur. Implementation of oral vaccination in free-ranging carnivore hosts demonstrates the feasibility of disease abatement in particular wildlife populations, such as demonstrated in Europe and North America, with an enhanced need for application to developing countries in the Americas, Africa and Eurasia [89]. Hence, mass vaccination of dogs is a comparatively inexpensive and ethical way to control the disease in animals and to prevent human exposure and illness, especially in resource-limited countries [53]. More research is needed to assess the dynamics of dog-to-human rabies transmission and the frequency of revaccination programs needed because of turnover in dog populations and continued risk for reintroduction of rabies from outside sources to unvaccinated dogs [53].

The impact of emerging diseases such as rabies can be minimized through a well-prepared and strong public health system and similar systems developed by the livestock, wildlife and food safety sectors. National animal disease emergencies, especially those that spill over to affect human health, require a whole-of-government approach for effective disease containment. As it is highly likely that zoonoses and animal diseases with the potential to affect human health will continue to emerge, surveillance and response systems for emerging zoonotic diseases will need to be strengthened and maintained at national and international levels [71]. Applied research, linked across the human, livestock and wildlife sectors, is needed to inform preparedness planning and the development of evidence-based approaches to zoonotic disease prevention and control [71].

Coordinated actions to confront the serious rabies public health and economic problems should be undertaken by affected countries, with the assistance of international organizations, under conditions that are suitable for each country [90]. More precautionary measures for travelers and public health strategies to prevent the re-introduction of rabies in the country where eradication has been achieved should be put in place. Educational efforts are required in light of the lack of understanding of the dismal consequences of rabies among travelers [86]. Guidelines addressing the infectious disease risks associated with exotic animals that may help raise awareness of the risks and decrease the demand for exotic animals have been published [91]. However, no single agency can solve this problem alone; it is only through partnership with other federal agencies, wildlife associations, veterinary medical associations and private industry that we will be able to better control the global movement of animals and reduce the risk of introducing emerging infectious diseases into new locations [66].

Public health implications of African rabies-related lyssaviruses should be recognized by laboratory workers, researchers, veterinarians, wildlife personnel, gamekeepers and pet owners. A better understanding of the epidemiology of these viruses is vital and can only be achieved by improved surveillance and awareness [19]. It is recommended for public health authorities to (1) consider modernizing their vaccine manufacturing method because the level of immunity induced by the current vaccine is comparably low, (2) conduct frequent vaccination campaigns to maintain high levels of vaccination coverage and (3) actively manage the domestic dog population, which is largely responsible for rabies maintenance [4]. According to Rupprecht *et al.* [12], society must recall that despite the recent recognition of other important emerging infectious diseases, none exceed the case fatality rate of rabies. Given the clear relevance of rabies in public health, agriculture and conservation biology, substantive international progress must continue towards enhanced public awareness, human rabies prevention, wildlife rabies control and canine rabies elimination, with renewed collaborative vigour [12]. However, according to Tao *et al*. [63], multidisciplinary studies are required to improve rabies surveillance to identify potential alternative sources of human infection. Indeed rabies is a widely distributed zoonotic disease of major public-health importance and an emerging as well as re-emerging microbial and global health threat but a preventable problem. Surveillance strategies for rabies viruses and other rabies-ralated viruses in developing countries of the world especially, Africa must be improved to better understand the epidemiology of this virus and to make informed decisions on future vaccine strategies.

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