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Review

Control and prevention of canine rabies: The need for building laboratory-based surveillance capacity ☆

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ABSTRACT

Dogs are the source of more than 99% of human rabies virus infections in endemic regions. Without post-exposure prophylaxis, almost all cases are fatal, making rabies the most lethal infectious disease. Tens of thousands of deaths are reported annually, but the official figures are believed to be gross underestimates. Controlling canine rabies, especially in free-ranging dogs, is the first priority to reduce the burden of human disease. Because of their limited medical infrastructure, most endemic countries lack the laboratory facilities needed to diagnose human cases of viral encephalitis. Moreover, the veterinary sectors are often unable to undertake systematic surveillance and reporting of rabies in animals. Without an adequate and functioning risk assessment system that is primed for use, rabies will remain a 'neglected' and omnipresent disease, especially in poverty-stricken regions of the world. Fortunately, experience with the elimination of canine rabies from many industrialized countries has shown that these barriers are not insurmountable. Successful rabies prevention and control strategies that prove the absence of the disease depend on laboratory-based surveillance, rapid data reporting and an adequate system of risk assessment. Future control and prevention programmes should therefore coordinate the development of these key factors, creating synergies to eliminate rabies at its animal source. This article forms part of a symposium in *Antiviral Research* on the global elimination of canine rabies.

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1. Introduction: the global burden of rabies

Rabies is a neglected zoonotic disease that causes severe and long-lasting societal and economic burdens. Its implications are especially apparent in poverty-stricken less-developed countries,

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and are a significant public health threat for two-thirds of the world's population, being endemic across most of Africa and Asia (Fooks, 2005; Hampson et al., 2008). Rabies is generally considered to be a fast-moving transboundary disease that does not respect borders and is the most important human zoonosis causing tens of thousands of deaths per year, mostly in children (Rupprecht et al., 2008; WHO, 2005).

The case fatality rate of human rabies is the highest of all infectious diseases; once clinical disease develops, the resulting illness is almost uniformly lethal. Insufficient financial resources, a weak health care infrastructure and inadequate reporting systems all contribute to under-reporting of the disease. In addition, more rigorous public disclosure is urgently needed to determine the true global burden of rabies (Fooks, 2005; Knobel et al., 2007). This lack of empirical data has been a principal cause of the low prioritization of rabies control in endemic countries (Rupprecht et al., 2008).

In this article, we review obstacles to the elimination of canine rabies in resource-limited countries, and establish the critical role of validated diagnostic tests and surveillance systems in the management of rabies. Our paper forms part of a symposium in *Antiviral Research* on the global elimination of canine rabies. Other articles published to date provide a general overview of the problem (Meslin and Briggs, 2013), describe the potential economic benefits of eliminating the disease (Shwiff et al., 2013) and the role of public-private partnerships in rabies control efforts (Taylor, 2013).

2. Rabies: virus and disease

Rabies is caused by viruses in the genus *Lyssavirus* in the family *Rhabdoviridae*, order *Mononegavirales* (Dietzgen et al., 2011; Freuling et al., 2011; Marston et al., 2012). Each of the 12 recognized lyssavirus species has its own distinct geographic and host range distribution. Only the prototype species, rabies virus, is detected in domestic and wild animals worldwide.

Canine rabies has been eliminated from many regions through veterinary service initiatives, including the mandatory registration and vaccination of dogs and requirements for responsible dog ownership (Blanton et al., 2012; CDC, 2007). Oral vaccination campaigns for wildlife have also removed the threat of sylvatic rabies from carnivores in some areas (Muller et al., 2012). However, despite successes in Western Europe and parts of North America (MacInnes et al., 2001; Müller et al., 2012), rabies virus continues to circulate in independent epidemiological cycles in wild carnivores in other regions. Lyssavirus species and other zoonotic pathogens in bats continue to emerge as a public health threat (Banyard et al., 2011; Cutler et al., 2010; Gilbert et al., 2012).

3. The burden of rabies in Asia

The human rabies burden is highest in Asia, with most deaths occurring in India (Burki, 2008). This situation reflects the relative lack of systematic control and prevention initiatives, including surveillance and response systems. However, even though rabies is a major public health problem in India, it is only one of many infectious diseases threatening humans: cholera, viral hepatitis, leptospirosis, anthrax, tuberculosis, malaria and HIV infections also impose a heavy burden. Because vaccine-preventable diseases, especially in children, are the first public health priority (John et al., 2011), rabies and other zoonoses tend to be neglected, as they are not seen as the responsibility of either human or veterinary health care providers.

The most recent attempt to quantify the burden of human rabies in India concluded that its incidence was 2 per 100,000 population, giving an annual total of more than 20,000 deaths (Burki, 2008; Sudarshan, 2007). The key priorities in the fight against rabies are enhanced laboratory capabilities, improved access to modern vaccines, enforcement of responsible dog ownership, and enhanced public education and awareness of the disease. With an emerging global economy, India clearly must implement mechanisms to reduce and eliminate rabies. The first step will be the establishment of an official OIE reference laboratory in the Indian subcontinent region. The successful partnership between the existing WHO collaborating center for rabies in India (Bangalore) and an OIE reference laboratory would enhance surveillance activity and reporting of rabies cases in humans and animals to international organisations.

The populations of other Asian countries suffer from a similar rabies burden and as in India dogs are the principal reservoir. In China, for example, the number of human infections has increased exponentially over the last 15 years, attributed to an under resourced veterinary infrastructure, lack of knowledge of transmission dynamics, inefficient dog control and poor vaccination coverage (Hu et al., 2009). Of the estimated 130 million dogs in China, more than half are in rural areas; as a result, human rabies is a major public health problem (Montgomery et al., 2012). Recent studies of canine rabies dynamics in China have estimated a basic reproduction number (R_0) of 2, and predicted that, even though human cases are now decreasing, they will rise again before 2030 if measures are not taken to reduce the dog population and increase vaccination coverage (Zhang et al., 2011). In neighboring Nepal, a coordinated approach has been taken with veterinary laboratories positioned in key areas across the country (Fig. 1). Virus isolates genetically typed from Nepal illustrate how the regular movement of disease across land borders precludes implementation of efficient control and prevention strategies. Interestingly, a comparison of reported cases with active surveillance and models of rabies incidence based on dog bites suggest that the true incidence of rabies may be 100 times what is reported to authorities (Knobel et al., 2005; Pant et al., 2011). As well as being problematic to the local population, the threat of rabies has been identified as a key environmental hazard for travelers to the area (Boggild et al., 2007; Pandey et al., 2002). At least in Nepal, the veterinary services are in a position, with the necessary support, to establish a surveillance network using existing facilities (Fig. 1).

To reduce rabies in humans, authorities should make the control and prevention of canine rabies a public health priority (Meslin and Briggs, 2013). The overall national strategy should include improved animal surveillance through laboratory diagnosis, a more rapid response to human exposures (with provision of post exposure prophylaxis, PEP) and education of the public and health care providers (Montgomery et al., 2012; Meslin and Briggs, 2013). The supply and quality of human rabies vaccines have also been a problem in China; the use of counterfeit vaccines has caused fatalities and reduced the population's willingness to be vaccinated (Hu et al., 2008).

The rabies situation in Cambodia is especially tragic. Because access to PEP is rare, patients are usually not hospitalized following dog bites, and die in their homes (Ly et al., 2009). In 2007, the estimated number of deaths from rabies exceeded those from malaria and dengue. The Pasteur Institute in Phnom Penh is the only diagnostic laboratory in the country capable of providing free PEP and undertaking postmortem diagnosis in humans. As in so many areas where canine rabies is enzootic, a national system of diagnostic evaluation and reporting is required, together with surveillance initiatives to measure the true impact of the disease (Dodet et al., 2008; Ly et al., 2009).

Many island nations have succeeded in eliminating rabies, but some still struggle with the disease. This is most evident where deficiencies in the veterinary sector preclude coordinated control and prevention efforts. One such area is the Philippines, where ra-

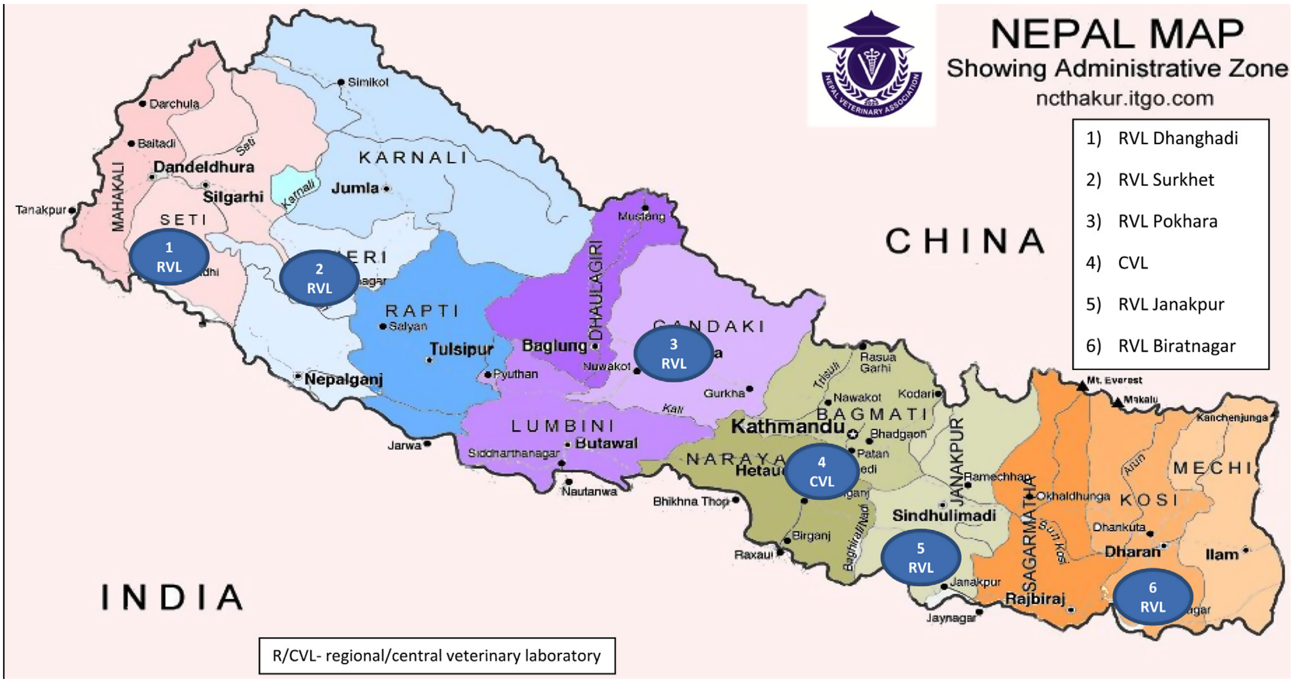

Fig. 1. Laboratory network for rabies surveillance in Nepal. Five regional laboratories are responsible for testing samples within their specific region. They support a National Reference Laboratory in Kathmandu, which undertakes confirmatory diagnostic testing and further characterization of positive samples. Due to the frequent movement of rabies across land borders, samples are also tested from animals that have been transported from neighbouring countries. Canine rabies control strategies would be more feasible if samples from Nepal were systematically analyzed to confirm the viral clades in circulation, which would assist in the overall goal of eliminating canine rabies in Southeast Asia.

bies remains a threat to the human population (Estrada et al., 2001). A recent retrospective study in Manila highlighted the difficulty of assessing suspected rabies patients in a resource-limited setting, and concluded that the true disease burden may be 10-50% higher than reported (Dimaano et al., 2011). Together with Tanzania and Kwa-Zulu Natal in South Africa, the Philippines has been targeted for new initiatives by the Global Alliance for Rabies Control and the Bill and Melinda Gates Foundation, which aim to demonstrate the feasibility of eliminating canine rabies in a resource-limited setting (Anonymous, 2008; Alliance for Rabies Control, 2012; WHO, 2010, 2013).

Although networks of rabies experts exist in Asia, their resources are limited; input from regional and national public health authorities will be required to increase their impact. The Asian Rabies Expert Bureau (AREB), founded in 2004, is an informal network of experts from 12 countries, which aims to eliminate human rabies deaths from Asia. Using the goals of the AREB as a framework, and with guidance from the WHO, several Asian countries have resolved to eliminate human rabies by 2020. Achieving this goal will require raising awareness, educating the public and new reporting and surveillance initiatives.

To support country-based initiatives aimed at increased rabies awareness, the AREB recently surveyed some 4000 animal bite victims from eight countries, and found that the situation of such patients could be markedly improved through education on appropriate wound care and timely consultation with a rabies prevention center (Dodet et al., 2008) However, the nearest primary health centre is often prohibitively distant, and its medical staff are unlikely to have access to a diagnostic laboratory or be able to provide PEP. Additional resources are clearly required (Estrada et al., 2001; Matibag et al., 2009).

A similar network, the Middle East and Eastern Europe Rabies Expert Bureau (MEEREB) network that was established in 2010, has improved regional collaboration (Aylan et al., 2011). Surveillance and reporting of rabies in the Middle East is variable, with many Middle East countries collating and reporting human rabies cases, but few reporting animal rabies (Aylan et al., 2011; Seimenis, 2008). Iraq is one example where there is a national system for reporting human rabies (albeit based on clinical diagnosis) but no systematic approach for animal rabies surveillance (Horton et al., 2013).

4. The burden of rabies in Africa

The true impact of rabies in Africa remains undefined. Although the number of countries reporting laboratory-confirmed cases of human rabies has decreased over the past 10 years (WHO, 2010), studies predicting the true number of human cases using indirect measures demonstrate that in Africa rabies is also under-reported because of poor surveillance and reporting structures (Fooks, 2005; Knobel et al., 2005). The virus is sporadically detected in wildlife, but canine rabies poses the greatest threat to humans. An improved understanding of dog ecology in Africa is therefore essential to the success of rabies control and prevention through vaccination campaigns (Kayali et al., 2003; Lembo et al., 2010; Perry and Wandeler, 1993; Wandeler et al., 1993). Region-specific studies, such as those in Tanzania, have improved rabies surveillance and control (Beyer et al., 2011; Cleaveland et al., 2010). A recent study in Uganda has also emphasized the need for active surveillance of animal bites and improved data on canine rabies, to improve mortality estimates and determine the true disease burden (Fevre et al., 2005).

Fortunately, recent initiatives have begun to improve the situation in many areas with the Southern and East African Rabies Group (SEARG), the African Rabies Expert Bureau (AfroREB) and the Rabies in West Africa (RIWA) group being networks dedicated to the fight against rabies. A recent AfroREB report stated that reliable data on the burden of rabies are still needed for informed decision-making and to set priorities. Unfortunately, rabies is diagnosed only clinically in most African countries, as few have facilities for laboratory confirmation. It is important to make rabies a notifiable disease in such countries (Anonymous, 2008). One future objective is collaboration between these African networks to create a pan-African approach to improve surveillance and reporting strategies.

5. Obstacles to rabies control and prevention

Controlling and preventing rabies in dogs is crucial to preventing the disease in humans (Coleman and Dye, 1996). Showcase initiatives have demonstrated that the elimination of canine rabies from Africa and Asia is epidemiologically and practically feasible, through mass vaccination and enforcement of responsible dog ownership (Durr et al., 2009; Kaare et al., 2009; Zinsstag et al., 2009). However, even though the tools are available, a number of obstacles prevent a coordinated approach to the global elimination of canine rabies, including: a lack of awareness and education of the public health and veterinary sectors; the absence of diagnostic facilities; inadequate surveillance and reporting systems; limited access to modern vaccines; and failures of responsible dog ownership (Sudarshan, 2007; Burki, 2008; Dodet et al., 2008; Zhang et al., 2011). The lack of effective control of canine rabies in developing countries is often attributed to low prioritization, epidemiological and operational constraints and insufficient financial resources.

Because effective rabies control and prevention programmes require reliable information on disease occurrence, they should be guided by modern epidemiological insights and driven by laboratory-based surveillance (Rupprecht et al., 2006a). Improved local diagnostic capacity is essential to achieve adequate canine vaccination coverage and to assess the impact of control and elimination efforts (Lembo et al., 2010). Since these factors are interlinked, the implementation of one will positively enhance the others.

In addition to mechanisms to reduce rabies in domestic dogs, the availability of simple and affordable diagnostics will enhance reporting and identify areas where the disease is most burdensome. In many countries, rabies diagnosis still relies on clinical observations. In Bangladesh, for example, the true disease burden cannot be accurately determined, because human cases are reported without confirmatory laboratory tests, and surveillance systems are not available. As in other endemic countries, the first priority for the development of a national rabies control program is the establishment of a diagnostic laboratory infrastructure (Hossain et al., 2011, 2012). As technical advances make diagnosis more rapid, accurate and cost-effective, it will become easier to initiate such programs in resource-limited settings (Rupprecht et al., 2006a).

6. Rabies control and prevention requires rapid and accurate laboratory-based diagnosis

Before discussing recommendations for rabies surveillance and diagnosis, we should provide some definitions. The OIE defines *surveillance* as the systematic ongoing collection, collation, and analysis of information related to animal health, and the timely dissemination of that information to those who need to know, so that action can be taken (OIE, 2012). A *case of rabies* is defined as any animal infected with rabies virus, as determined by the tests prescribed in the Terrestrial Animal Health Code (OIE, 2012). Suspect and probable cases of rabies in animals are usually defined at the national level. In the context of this review, *diagnosis* refers to the clinical and laboratory information that lead to confirmation of a case of rabies.

The lack of laboratory capacity in endemic areas means that rabies is usually diagnosed clinically, but because the disease has no pathognomonic signs and its manifestations are highly variable, this approach is often inaccurate. For example, a study in Malawi found that three of 26 patients diagnosed with cerebral malaria actually had rabies (Mallewa et al., 2007). The differential diagnosis of all cases of encephalitis in rabies-endemic countries should therefore include rabies (Fooks et al., 2009).

Rabies can, however, be diagnosed clinically when an animal bite is followed by a compatible neurological illness. It is difficult to accurately assess the rabies status of dog populations without sufficient testing of suspect dogs. The diagnosis should also be considered when a patient without a history of a bite develops an acute, unexplained neurological disease, especially if it progresses rapidly to coma and death (Rupprecht, 2006). Globally, hundreds of thousands of persons are potentially exposed to rabies each year, and most require some form of PEP. The inability to perform diagnostic evaluations of suspect animals thus results in inappropriate estimates of the level of vaccination required and major financial costs (Shwiff et al., 2013). From 20 to 40,000 people in the US may receive PEP each year (Christian et al., 2009), but post exposure care is scarce in resource-limited settings. In Tanzania, for example, where human rabies cases are greatly under-reported, the number of dog bites can be used to estimate the disease burden and monitor epidemiological trends (Cleaveland et al., 2002).

Even when local facilities and infrastructure make diagnostic testing possible, the cost of even the simplest tests places a further burden on the health system. Rabies diagnosis often requires costly and time-consuming procedures, such as the OIE-prescribed fluorescent antibody test (FAT), with the potential for a confirmatory diagnosis by virus isolation (Table 1). Although it is rapid, sensitive and specific, the FAT relies on expensive FITC-labeled anti-rabies antibodies and a fluorescence microscope, often precluding its use in resource-limited settings. Virus isolation in tissue culture also requires laboratory capabilities that are usually unavailable where they are most needed. Fortunately, the direct, rapid immunohistochemical test (dRIT) for rabies now provides a more economical alternative to the FAT (Lembo et al., 2006). Simpler and less expensive diagnostic platforms are needed to enhance laboratory capacity in rabies-endemic regions (Fooks et al., 2009).

7. The need for improved surveillance

Experience from regions where rabies has been eliminated shows that evidence-based diagnostic and surveillance strategies are needed to determine the distribution and prevalence of different lyssavirus species in Africa and Asia. Such strategies must involve the collation of animal disease data and its provision to public health authorities, to enable them to develop effective policies (Lembo et al., 2011; Zinsstag et al., 2009). Once surveillance mechanisms are in place, it is essential to ensure the quality and reliability of the data and its dissemination within an expert network (Aylan et al., 2011). Importantly, effective surveillance permits early case reporting, which is vital for timely responses and informed decision-making. The combination of laboratory-based surveillance, enhanced public awareness and strategic utilization of potent, inexpensive vaccines is essential for rabies control and prevention (Murray and Aviso, 2012; Fooks, 2005). Once established, an animal surveillance system can be customized and implemented to support the elimination of both canine and human rabies (Fooks et al., 2009; Townsend et al., 2012).

Rabies surveillance should include both ‘passive’ and ‘active’ laboratory-based strategies. A ‘passive’ surveillance strategy offers a continuous monitoring of disease occurrence within a population by reporting notifiable diseases on a case-by-case basis. Passive surveillance is advantageous because it occurs continuously, and it requires few resources. In contrast, ‘active’ surveillance is a pro-

Table 1
Comparison of tests currently used in rabies diagnostic testing. Reproduced with permission from (Harkess and Fooks, 2011).

Test	Use	Unit cost	Turn-around time	Sensitivity	Specificity
Fluorescent antibody test (FAT)	'Gold standard' test	Cheap	2–4 h	Medium	High
Rabies tissue culture infection test (RTCIT)	Confirmatory test	Moderate	5 days	High	Medium
Mouse inoculation test (MIT)	Confirmatory test	Expensive	28 days	High	Medium
Reverse transcription-polymerase chain reaction (RT-PCR)	Screening	Cheap	2 days (including RNA extraction)	High	High
Real-time PCR	Screening	Cheap	1 day (including RNA extraction)	High	High

active strategy for laboratories to disseminate information about notifiable diseases. While the latter method is more costly and labor intensive, it tends to provide a more complete estimate of disease frequency. A robust surveillance system should prioritize data collection, recognising the need for cooperation through a 'One Health' agenda (Fooks, 2007; WHO, 2008; Fisman and Laupland, 2010). An effective system should also be characterized by standardisation and decentralisation, emphasizing locally-based efforts, and by coordination, interpretation and integration of different approaches. To support standardization, the OIE has proposed a pathway to sustainably improve the compliance of veterinary services, setting international standards as a continuous process of reflection and improvement. Its key components are performance, vision and strategy. By following this pathway, veterinary services will acquire the knowledge and skills needed to control and prevent rabies (Murray and Aviso, 2012).

Where the technology is available, surveillance data can be transferred to a real-time, web-based reporting and communica-

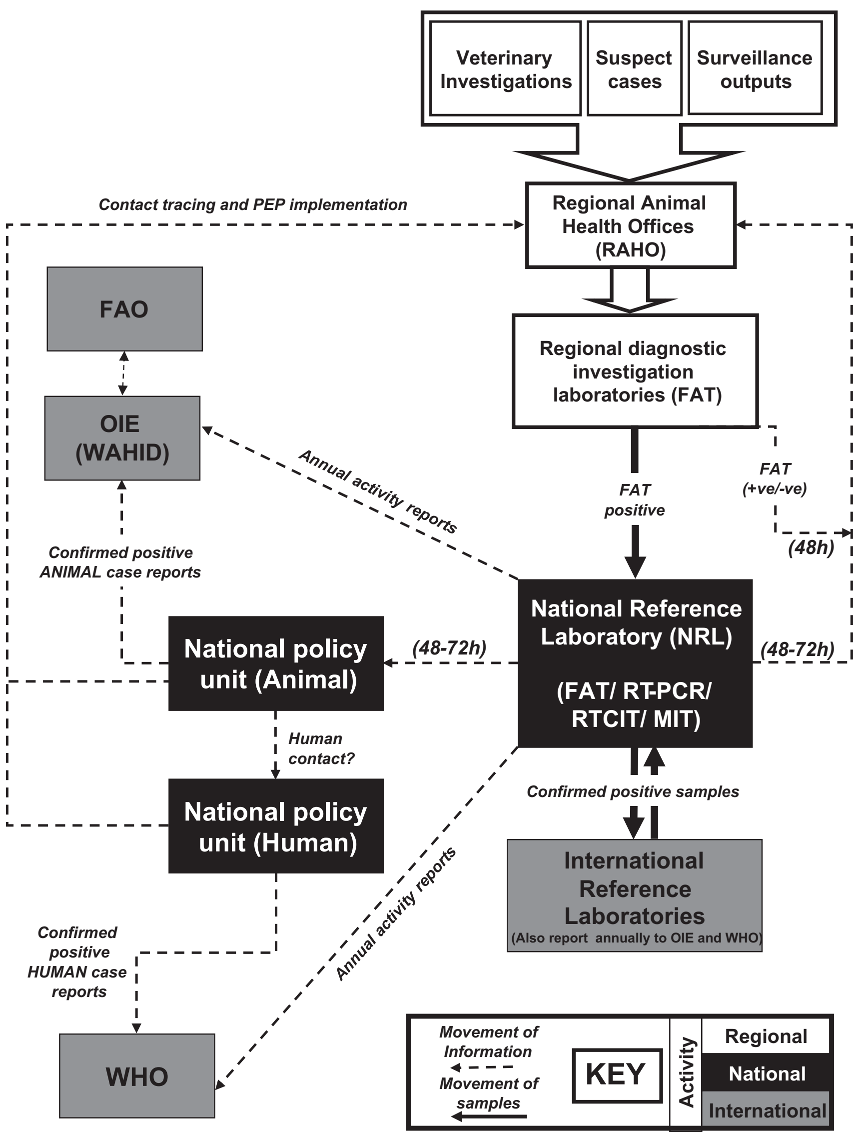

Fig. 2. Flowchart demonstrating a multi-sectorial, integrated approach to rabies surveillance. International reporting systems, such as the Rabies Bulletin Europe (RBE) and the OIE World Animal Health Information System (WAHID) interface, depend on consistent disease reporting, backed up by confirmatory laboratory diagnosis in participating countries. Because of the severity of canine rabies, it is imperative to make an initial clinical diagnosis, followed by laboratory-based confirmation to distinguish the infection from other diseases. Human postexposure prophylaxis is highly dependent on an accurate and rapid diagnostic test result from a suspect animal. A number of different technologies for the diagnosis of rabies have been approved by the The World Organisation for Animal Health/Office International des Epizooties (OIE) (Fooks, 2011). Test results are shared with the World Health Organization (WHO) and the Food and Agricultural Organization (FAO).

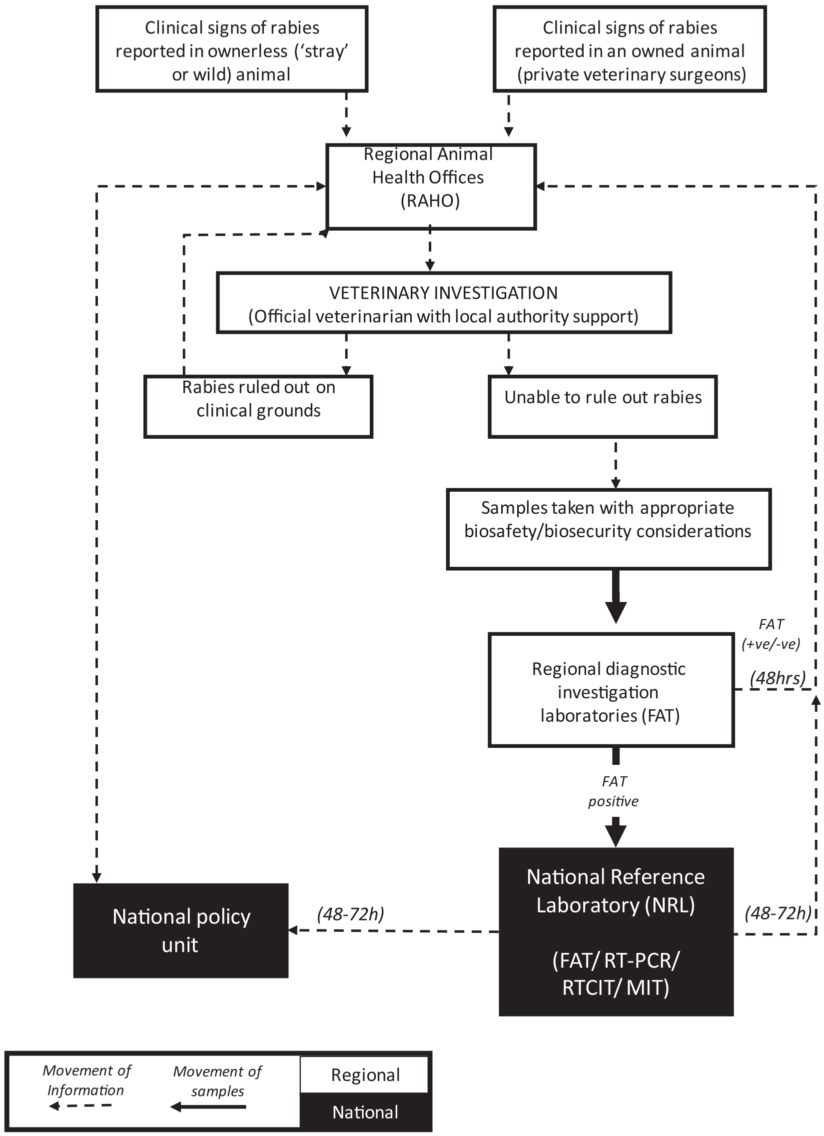

Fig. 3. Flowchart demonstrating an example of a coordinated national approach to a surveillance system for rabies in animals. Tests for rabies virus antigen include direct detection in tissues by the fluorescent antibody test (FAT) and indirect assays through the rabies tissue culture infection (RTCIT) or mouse inoculation tests (MIT). More recently, the use of reverse-transcription polymerase chain reaction (RT-PCR) to detect viral RNA allows for high-throughput, rapid analysis of samples (Fooks et al., 2009). Brain tissue is the most reliable specimen for detecting live virus. Sampling methods vary for animal species. In small mammals such as bats and mice, removing the entire brain and testing a homogenate by FAT, RTCIT, MIT, or PCR is highly sensitive and reliable. In larger mammals such as dogs, the pons, medulla and thalamus are the most reliable portions of the brain to sample, but a pool of tissues including brain stem is also acceptable.

tion system, using a Geographic Information Systems (GIS) linked to internet-based mapping tools (Rupprecht et al., 2006b). Reporting systems, such as the Rabies Bulletin Europe (RBE) (Freuling et al., 2012) and the OIE World Animal Health Information System (WAHID) interface, depend on consistent disease reporting, backed up by confirmatory laboratory diagnosis by participating countries, both of which are often lacking. Their dependence on different sectors for the development and reporting of case data demonstrates the need for a multi-sectoral, integrated and inter-disciplinary approach (Fig. 2). Reliable systematic surveillance of human rabies deaths and animal prevalence at the national level (Fig. 3) would markedly improve knowledge and response to rabies, and is urgently needed.

8. Conclusions and future perspective

More than 30 years ago, the global eradication of smallpox demonstrated that well-supported surveillance campaigns are essential to reduce and potentially eliminate an infectious disease (Fenner et al., 1988). Fortunately, a great deal of progress has been made against rabies. Animal management, including public education, responsible dog ownership and vaccination strategies, have been identified as the keystone of modern control programs. Using this model, the connection between rabies in dogs and humans has been clearly demonstrated through the successful elimination of canine rabies from Western Europe and parts of the Americas (WHO, 2010). Similar campaigns to monitor rabies and vaccination in dogs in the developing world are receiving international support. These "showcase" initiatives have demonstrated that it is possible to eliminate rabies from terrestrial populations. Information on these initiatives can be obtained from the web sites of the Rabies Blueprint (http://www.rabiesblueprint.com/) and World Rabies Day (Briggs and Hanlon, 2007) (www.worldrabiesday.com).

A number of factors will increase the potential for successful rabies elimination programmes. First, rabies must be made a notifiable disease in all countries. Where the necessary infrastructure does not exist, governments must generate facilities for reporting and surveillance. Veterinary and medical sectors should coordinate their resources to respond to suspect cases. Importantly, the successful establishment of functional reporting systems requires mechanisms for practical laboratory-based surveillance. The enhancement of sensible pet care, including vaccination, registration, routine supervision and population planning, is one of the most cost-effective elements (Rupprecht et al., 2006a).

Systems must be implemented to accurately monitor the burden of rabies in local areas; those data can then be used to influence policy, ensuring that resources are allocated in the most efficient and cost-effective manner. Monitoring relies principally on reliable, sustained surveillance and reporting; appropriate diagnostic capabilities for animal and human cases; and an accurate epidemiological assessment of the prevalence of rabies in dogs and humans. This information can drive risk-assessment systems in local areas, ensure compliance and influence policy. The confirmatory diagnosis of all suspect cases is essential for these desired outcomes (Fig. 3).

Efficient reporting and surveillance systems are essential for targeted rabies vaccination and elimination strategies. However, limiting factors including the lack of coordinated initiatives, dog ecology data and financial support for vaccination campaigns all hamper elimination prospects. However, all of these obstacles can be overcome through international coordination under the 'One Health' initiative (Fooks, 2007), and especially by working collectively within public-private partnerships (Taylor, 2013). Importantly, the vast majority of domestic dogs are accessible for vaccination, and educating their owners in the dangers of rabies will further reduce the burden. However, enhanced local facilities for surveillance and diagnostics are still essential for control and elimination initiatives. The implementation of government led cross-discipline efforts in the establishment of dog vaccination campaigns are critical in linking the veterinary and medical sectors as part of the 'One Health' initiative to effectively fight rabies.

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