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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.

Contents

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-