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Review

Eliminating canine rabies, the principal source of human infection: What will it take?

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ABSTRACT

More than 50,000 people die of rabies each year; most are children in developing countries, and almost all have been bitten by dogs. Eliminating canine rabies throughout the world would save thousands of lives and would reduce the economic impact of the disease by dramatically reducing the requirement for post-exposure prophylaxis (PEP). Lengthy experience in the industrialized countries and ongoing programs in Latin America, Africa, and Asia have shown that the elimination of rabies in dogs is an achievable goal. The presence of canine rabies in developing countries is associated with poverty, and most deaths occur in the lowest socioeconomic sectors. To be successful, national rabies control programs should share responsibility with local communities for prevention and control activities and maintaining disease-free status. Legislation should be adapted to local conditions and the realities of dog ownership. While the provision of PEP to all bite victims is affordable in many countries, it is usually beyond the capacity of impoverished nations, which deal with many other health priorities. Ministries of health should provide PEP, either free or with a charge preferably at a subsidized price, replacing the current system in many countries, in which biologics are sold by government-owned and private clinics at a cost beyond the means of bite victims. The public health sector should assume responsibility when animal control strategies are not effectively implemented or when PEP is not administered correctly or is not available. A global strategy is needed to identify gaps in surveillance and diagnosis, improve access to PEP and enhance canine immunization and population management. Such approaches based on a "One Health" model should be coordinated across regions, and should extend control efforts to other dog-related zoonoses. This article introduces a symposium in *Antiviral Research* on the elimination of canine rabies.

Contents

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1. Introduction

When Louis Pasteur successfully used an experimental live attenuated rabies vaccine to treat a child severely bitten by a rabid dog in 1885, he triggered a series of scientific events that would lead to the development of safer and more effective methods to reduce the number of human rabies deaths. We have estimated that the introduction of postexposure prophylaxis (PEP) for rabies has saved more than 20 million lives since 1885 (Meslin, 2012). However, despite the existence of effective PEP, rabies continues to take the lives of the poorest segment of the population in developing countries. Millions of exposures still occur annually, and many are untreated, resulting in tens of thousands of deaths (Knobel et al., 2005; Rupprecht, 2004; WHO, 2005).

In Africa and Asia, where more than 99% of all human cases occur, the domestic dog is the most important source of transmission. The disease disproportionally targets children: between 45 and 60% of all dog bites and human rabies cases occur in children less than 15 years of age (Abubakar and Bakari, 2012; Liu and Ertl, 2012; Osaghae, 2011). Eliminating the circulation of rabies virus in dogs in Africa and Asia would prevent more than 99% of human cases (Lembo et al., 2010; WHO, 2012).

This article introduces a six-part series in *Antiviral Research* examining a strategy to eliminate canine-transmitted human rabies. The authors of these papers believe that it is within our grasp to reduce the global burden of rabies, utilizing currently available tools. Examples of successful canine rabies elimination programs prove that it is possible to prevent most human rabies cases by targeting the major source of infection (Blancou, 2008; Hampson et al., 2007). Because some 75% of infectious diseases in humans are zoonotic, the authors consider that a successful, sustainable rabies prevention program based on a "One Health" approach can serve as the perfect example for governments to build strategies to reduce the burden of other zoonoses (Arambulo, 2011; Wright et al., 2008).

The present article briefly reviews the global epidemiology of canine rabies, its prevention in humans, building sustainable programs for the control and elimination of canine rabies, and future directions for program development. Two accompanying papers examine the economic benefits to developing countries of eliminating canine rabies (Shwiff et al., 2013) and the value of public–private partnerships for rabies prevention (Taylor et al., 2013). Three further articles will focus on rabies control programs in Latin America; the need for national systems of diagnosis, surveillance and risk assessment; and current and future tools for global rabies elimination.

2. Rabies: a brief overview

Rabies is a viral encephalitis that is present on every continent except Antarctica. It has the highest case fatality rate of any infectious disease (WHO, 2010; Rupprecht et al., 2002). Once clinical symptoms are present, humans with rabies almost always die. However, because it is not a reportable disease in most resource-poor countries, and because most patients belong to lower socio-economic groups, the actual number of rabies deaths that occur each year is not known (Lembo et al., 2011; Sudarshan and Ashwath Narayana, 2010). Also, paralytic rabies is often misdiagnosed as another disease, such as malaria or Guillain–Barré Syndrome, thus helping to mask its true global burden (Hemachudha et al., 2002; Mallewa et al., 2007). Such under-reporting has resulted in rabies remaining low on the list of public health priorities for many poor countries.

The lack of effective rabies prevention programs all too often leads to a lack of awareness among the general public of how to prevent the disease after an exposure, so that patients with limited financial resources seek ineffective treatments from local healers. Adding to this problem is the fact that anti-rabies biologicals are often unavailable to those who cannot afford to travel to clinics and purchase them (Warrell et al., 2008).

3. Pre- and postexposure prophylaxis

Human rabies vaccines are among the few biologics that can be used before or after exposure. The World Health Organization (WHO) recommends that pre-exposure prophylaxis (PreP) be administered to persons such as veterinarians, who are at increased risk of exposure (WHO, 2005, 2010). PreP is also a valuable tool for protecting populations in remote, high-risk regions, where prompt PEP is not immediately available. Pre-exposure vaccination is given as a three-dose series of intramuscular or intradermal injections on days 0, 7 and 21 or 28.

Rabies is an unusual disease, in that it can be prevented by prompt wound care and vaccination (WHO, 2010). Wounds inflicted by a suspect rabid animal should be thoroughly washed as soon as possible, following WHO recommendations. PEP includes a 4- or 5-dose series of injections of rabies vaccine, beginning as soon as possible after exposure (WHO, 2005, 2010). Four different vaccine regimens are currently approved by the WHO and the Advisory Committee on Immunization Practices (ACIP) for persons not previously immunized against rabies (Table 1); three are given intramuscularly and one intradermally. There are also three WHO-approved regimens for previously vaccinated individuals (Table 1). Rabies Immune Globulin (RIG) is also an important component of PEP. It should be injected into and around the wound site, ideally on the day of exposure or up to 7 days after the initial dose of vaccine.

Vaccines and RIG are the most important tools to prevent human rabies (Briggs, 2012). However, when governments invest solely in purchasing biologicals, without supporting other essential components of 'holistic' prevention and control programs, the cost of human rabies prevention will continue to escalate, without resolving the underlying problem. Based on current pricing strategies, the most effective and sustainable way to prevent almost all cases of human rabies in Africa and Asia is to eliminate the disease at its major source of infection, unvaccinated dogs (Wunner and Briggs, 2010; Brown, 2011; Wilde et al., 2012).

4. The role of dogs in human rabies

More than 99% of human rabies cases occur in Africa and Asia, where domestic dogs are the most important source of infection (Knobel et al., 2005; Rupprecht, 2004). Virtually 45–60% of dog bite injuries and human deaths occur in children under 15, who rarely understand how rabies is transmitted, and often do not know how to behave around animals, especially dogs living in the same household or community (WHO, 2005). Children who have been bitten or scratched by suspect rabid dogs may therefore not tell their parents or guardians, especially if they have been instructed not to approach animals that are not their own pets (Bhanganada et al., 1993; Bothra et al., 2011; Cleaveland et al., 2003).

Dogs can be protected against rabies by vaccinating animals at risk of exposure. Many canine rabies vaccines are produced around the world by a number of pharmaceutical companies, which provide specific recommendations regarding the age of dogs at primary vaccination and the timing of boosters. However, when mass vaccination programs are being implemented in developing countries, all dogs, including puppies, should be vaccinated whenever the opportunity arises (Lembo et al., 2012; Wandeler et al., 1993).

A number of countries successfully implemented large-scale vaccination programs to eliminate canine rabies during the past

Table 1
Pre- and postexposure vaccination regimens currently recommended by the World Health Organization and the Advisory Committee on Immunization Practices. ID: intradermal. IM: intramuscular. From (Manning et al., 2008; WHO, 2010).

Type of vaccination	Number of doses	Number of clinic visits	Route	Schedule (days)
Pre-exposure				
Routine	3	3	ID[a] IM[a,b]	0, 7, 21 or 28
Postexposure				
Essen	5	5	IM	0, 3, 7, 14, 28
Zagreb	4	3	IM	0 (2 doses in each deltoid) 7, 21
Reduced 4-dose	4	4	IM	0, 3, 7, 14
Modified thai red cross	8	5	ID	(2 doses on each day) 0, 3, 7, 28
Postexposure for previously vaccinated persons				
Two-dose	2	2	IM	0, 3
Four-dose	4	1	ID	(2 doses above each deltoid) 0

century, dramatically reducing the incidence of the disease in humans (Hampson et al., 2007; Rupprecht et al., 2008; Schneider et al., 2007, 2011). Canine variants of rabies virus have been eliminated from the USA, Canada, Western Europe, Japan, Malaysia, and Hong Kong. Great strides have also been made to eliminate canine rabies from Latin America. Although rabies virus continues to circulate in wildlife such as bats, raccoons, skunks and foxes throughout North and South America, it poses a more distant threat to humans, principally through contact between infected wild animals and unvaccinated pets (Noah et al., 1998; Arambulo, 2008; Castilho et al., 2010).

5. Canine rabies elimination programs

Targets for the elimination of dog and human rabies have been established for all Latin American countries by 2015 and for Southeast Asia by 2020 (ASEAN, 2008, 2012; PAHO, 2008, 2009; SEARO, 2012; WHO, 2012). In the latter region, a five-year plan (2012–2016) aims to halve the number of human rabies deaths. Such regional and national programs to prevent canine-transmitted rabies should not focus only on the purchase of human rabies biologicals. Sustainable control programs require strategic planning, focused on the concept of "One Health," which requires officials responsible for animal and human health to work together. As discussed in the following sections, planning should include political support, carefully orchestrated operational activities and improved use of state-of-the-art scientific methods to enhance data collection and surveillance (Gongal and Wright, 2011).

5.1. Political support

Political support from the highest levels of government is essential to ensure long-term commitment and financial support for all aspects of a canine rabies prevention program. Government officials must understand what is required to eliminate the circulation of rabies in the target area, and be willing to support the program for both the short and long term. One of the most important building blocks for an effective program is the establishment and enforcement of a regulatory and legal framework for canine rabies control (Lembo et al., 2011). This includes the development of national strategies, which will necessarily include representatives of appropriate national ministries such as health, agriculture, environment and education. Legislation must be in place at a national and local level to enforce dog vaccination policies.

As governments begin to develop canine rabies elimination programs, they should develop partnerships with local communities (Lembo et al., 2008, 2011, 2012). Neighborhoods benefit from eliminating the threat of rabies and citizens can help to implement and monitor programs. Local champions for canine rabies elimination are enthusiastic supporters when they are engaged as partners, providing hands-on support at a local level (Lapiz et al., 2012).

Governments must also be involved in public awareness programs that support responsible pet ownership, and do not promote the mass killing of dogs. Mass killing is not effective, alienates the general population and often creates conflict with international organizations (Kahn et al., 2008). It often causes dog owners to hide their dogs or move them to other areas, potentially promoting the spread of rabies. It is also inhumane to use strychnine to kill dogs. Not only does poisoning cause unnecessary pain and suffering, it can also pose a threat to humans and other animals where the poison is distributed. Instead of mass killing, rabies control programs should support the enforcement of international recommendations for the reduction of dog populations (Lembo et al., 2012). Reputable animal welfare organizations are often willing to provide training and assistance for dog handling, spaying and neutering. They can be valuable partners for national governments engaged in sustainable canine rabies control programs (Villa et al., 2010).

5.2. Operational activities

Canine rabies control programs must include experts from both the human and animal health sectors in their daily activities. In many countries, these departments are not connected, and they are often centered in separate locations, but it is essential that they work together. Although the immediate objective is to stop the circulation of rabies virus among dogs, protecting humans is the ultimate goal. Surveillance activities and reports of rabies in animals and humans must therefore be shared across departmental lines. Effective prevention also requires monitoring of dogs involved in potential human exposures. Increased surveillance is also essential to document decreases in the number of animal and human rabies cases. As adequate surveillance is put into place, it is also important to increase the capacity for public health officials to respond to emergencies, such as an outbreak of rabies in a zone where it had previously been eliminated, or the importation of an infected dog into a rabies-free zone.

Research has shown that canine rabies can be eliminated by establishing a 70% level of vaccination coverage (Davlin and Vonville, 2012; WHO, 2005). Ecology studies, including evaluation of the location of the dog population in the region, must be conducted before beginning a mass vaccination campaign. Information on how to set up and conduct such campaigns is freely available online (Andrade et al., 2008; Beran, 1982; Lembo et al., 2012).

Mass communication and awareness are critical for improving community support for rabies control programs, and to save the lives of persons exposed to rabid dogs. Almost every human rabies death has resulted from a lack of awareness that PEP should be administered as soon as possible, or from failure to follow WHO recommendations for wound washing and vaccination (Hemachudha et al., 1999; Wilde, 2007). As a result of the dissemination of prevention and control information and increased public awareness, the utilization of PEP often increases during the initial stages of a rabies control program. Increased access to rabies biologicals is therefore essential to protect exposed persons, in conjunction with dog vaccination.

5.3. Scientific methods

Data collection is a critical component of a successful canine rabies control program. Without accurate data, it is impossible to

evaluate progress and eventually confirm that rabies has been eliminated from the target area. The installation and utilization of an effective data management system must therefore be part of the program strategy from the beginning.

The program directors will ultimately decide what kind of data management system will be utilized. For example, different methods have been used to collect the initial dog population data that is required to plan a vaccination campaign and to ensure that sufficient vaccine is available. If the number and location of the existing dog population are not known, or if different departments use different methods to gather information, data may be missing or non-existent. As a consequence, essential information about vaccine coverage of the dog population will be only guesswork, resulting in program failure. In this regard, new cell-phone technology has begun to allow real-time transfer of information to a central data bank, where it is processed to monitor the stocks and usage of human and dog vaccines, report PEP and the outcome of vaccination campaigns (Halliday et al., 2012).

One of the most important points to be addressed in all canine rabies elimination programs is the ability to collect sufficient samples from suspect animals to adequately assess the presence of rabies. It is also essential to be able to determine the 'risk' of rabies to humans. This often requires an increase in laboratory capacity, so that all suspect rabid animals can be submitted for testing, and to monitor a decrease in infected animals. A national rabies reference laboratory should be responsible for training, data collection and ensuring the quality of other diagnostic testing facilities. Where possible, molecular analysis of submitted specimens should be conducted, to identify rabies virus variants circulating in the target area and establish accurate epidemiological maps detailing the presence and spread of the virus. Enhanced diagnostic testing and evaluation of epidemiological maps are critical components of the level of surveillance needed to ensure the elimination of canine rabies.

6. Building sustainable programs

Establishing a canine rabies elimination program in countries with large dog populations requires a major investment of time and money. However, the financial costs to support the increased manpower required for rabies reduction can dramatically improve public health, and can serve as examples for the prevention of other zoonotic diseases. As with any other public health investment, it is important to consider how sustainability can be built into programs from the beginning of the planning process. Establishing sustainability will entail different strategies in different regions.

Long-term government commitment is essential to ensure consistent and easy access to canine rabies vaccine, until the disease has been eliminated. Financial contribution to the cost of vaccination by dog owners can be considered to support sustainability; however, the success of this approach will depend on the local context and situation. Where paying for the veterinary care of dogs is not a common practice, or where financial contributions are set too high, vaccine utilization may be too low to achieve the coverage needed for effective rabies control. The impact of requiring owners to contribute to vaccination costs, and available options for differential contributions, based on an owner's capacity to pay, have received relatively little study. Further evaluation of these approaches would be beneficial. Where dog owners are unwilling or unable to pay at the level required for critical coverage, vaccination should be provided free of cost and balanced against its public health benefits, including reduction in expenditures for PEP.

Any sustainable program will require a high level of community involvement. Where feasible, incorporating information about rabies prevention into the school curriculum will help to educate children, who are most at risk of dog bites. Creating community volunteer associations to serve as 'rabies watchers' to report unattended dogs, dog bites, suspect rabid animals and other concerns is working well in the Philippines (Lapiz et al., 2012). Such associations help keep local citizens involved in their own program. Establishing partnerships between reputable international and local animal welfare organizations and government institutions can also assist in maintaining program sustainability, but there must be a good level of understanding between the organization and the government.

Program sustainability also depends upon enhanced surveillance, both before and after canine rabies has been eliminated from an area. The WHO and the World Animal Health Organization have declared that a country or an area may be considered rabies-free if no case of indigenously acquired infection has been confirmed in humans, dogs, cats or other species during the previous 2 years (Kahn et al., 2008; WHO, 2005). In regions where rabies has been eliminated from the resident dog population, infected dogs may occasionally be imported. When active surveillance is in place, such cases can be identified quickly, preventing the disease from re-emerging. The identification and follow-up of an imported case of canine rabies in a "rabies-free" zone should not be considered a program failure, rather it should be seen as a sign of success, since the program successfully detected the case and took appropriate action.

7. Future directions

Because almost all human cases result from the bite from an infected dog, the best way to reduce the global burden of canine-mediated human rabies is to eliminate canine rabies. This approach is much more cost-effective than attempting to expand the availability of PEP, or to integrate rabies vaccination into national immunization programs. Research focusing on humane methods to reduce the fecundity of dogs in countries where an overpopulation of free-roaming animals hampers disease control would be a major step forward. New research investigating the incorporation of a birth control product into rabies vaccines offers hope in the fight against rabies (Bender et al., 2009; Hiby, 2013; Massei, 2013).

Improved education of public health professionals and the public would help enhance basic understanding of rabies prevention. Novel educational methods are beginning to make progress in many countries. For example, Philippine educators have made remarkable strides by including rabies educational activities in elementary school modules (Lembo et al., 2011). However, because many children are not taught in a formal classroom setting, new approaches that could reach a wider population in endemic areas would save lives.

World Rabies Day continues to provide opportunities for communities and international health organizations to get involved in improving awareness of rabies (www.worldrabiesday.org). New communication tools have brought messages to more than 150 countries (Cleaveland et al., 2010). These activities should continue to be supported and individuals are encouraged to educate their own communities. Programs aimed at bringing together professionals from human and veterinary medicine to work together, using a 'One Health' strategy, to begin to develop programs to eliminate canine rabies. A free online resource that brings together all necessary information provides an excellent source of reference (Lembo et al., 2012).

A major cause of human rabies deaths is the lack of funds required for bite victims to travel to a clinic and buy vaccine (Hampson et al., 2011). Fortunately, the number of vaccine

injections and volume per injection site for effective PEP have diminished over the past 30 years, and it is expected that even shorter courses of PreP and PEP will be developed (Rupprecht et al., 2010). Such regimens have shown promising results, and should be further evaluated for possible inclusion in WHO recommendations (Khawplod et al., 2002, 2012; Shantavasinkul and Wilde, 2011). The cost of vaccination can also be lowered by applying PEP by the ID route, as is practiced in all public hospitals and clinics in India, the Philippines, Sri Lanka and Thailand, reducing the volume of vaccine by as much as 80% (Kamoltham et al., 2003). However, ID vaccination is currently available only in large clinics in major metropolitan areas, to which rural and poor populations of most countries do not have access. Substantial savings could also be achieved by acquiring human and dog vaccines at preferential costs, through a mechanism like that of the Global Alliance for Vaccines and Immunization, and by promoting technology transfer for local production.

The use of RIG is rare in Africa, Asia and rural regions in Latin America, due both to the cost of the product and the lack of awareness of most health workers that it is an essential component of PEP in cases of severe exposure. However, just as the large-scale production of rabies vaccines in cell culture has greatly expanded their availability, the manufacture of a cocktail of selected rabies monoclonal antibodies (mAbs) in large quantity, focused on the replacement of RIG, may similarly expand and promote the use of passive immunity in the next decade (Bakker et al., 2008; de Kruif et al., 2007; Goudsmit et al., 2006; Müller et al., 2009).

8. Summary

The most cost-effective strategy to reduce exposure to a disease is to eliminate the source (Zinsstag et al., 2009). For canine-transmitted rabies, this can only be accomplished through a 'One Health' strategy, in which officials responsible for animal and human health work together. This should be considered as a public health goal for Africa and Asia, the two continents currently bearing the brunt of the global rabies burden. We have the tools, we have the knowledge and we now have examples of successful, sustainable canine rabies prevention programs. The accompanying articles in this symposium provide an outline of the strategy required to eliminate human rabies caused by exposure to infected dogs throughout the world.

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