Antiviral Research 98 (2013) 291–296

Contents lists available at SciVerse ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Review

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

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ARTICLE INFO

Article history:
Received 16 November 2012
Revised 28 February 2013
Accepted 5 March 2013
Available online 21 March 2013

Keywords:
Rabies
Canine rabies
Lyssavirus
Rabies prevention
Canine-mediated human rabies
Rabies elimination

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.

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0166-3542/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.antiviral.2013.03.011

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

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