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Review

Current and future tools for global canine rabies elimination ☆

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ABSTRACT

Even though rabies is almost uniformly fatal, it is readily preventable with currently available tools. Vaccination is highly efficacious for the pre-exposure prophylaxis (PrEP) of rabies in humans and animals, and prompt postexposure prophylaxis (PEP) with vaccine and rabies immune globulin (RIG) can reliably prevent disease in humans. However, access to these tools and knowledge of their proper use are often limited, especially in impoverished, rabies-enzootic countries with the highest disease burden. In the absence of reliable diagnostic capacity and risk assessments, vaccines and RIG are often administered inappropriately, leading to chronic supply shortages and otherwise preventable deaths. Rather than focusing solely on human prophylaxis, it is more cost-effective over the long term to eliminate canine rabies in its natural terrestrial reservoirs. Because more than 99% of human rabies deaths result from dog bites, prevention efforts should focus on dogs. A versatile "One Health" strategy for canine rabies elimination should aim to create sustainable herd immunity in dogs, using proven vaccination strategies at the local level, coupled with community education and humane population management. Such strategies have succeeded in both developed and developing countries, and can be adapted to any locality. Numerous examples in Africa, Asia, and Latin America have shown that community-based, locally guided vaccination and education programs, based on a shared vision and long-term commitment, can eliminate canine rabies. Such programs should have specific goals and measurable outcomes, and should be conducted under the guidance of supportive governments, in collaboration with international partners and nongovernmental organizations. In addition to currently available tools, rabies prevention can be augmented by new dose-sparing human vaccine schedules, alternative routes of vaccine administration, monoclonal antibodies as an alternative to RIG, sensitive and specific point-of-care diagnostics and the development of canine immunocontraceptive methods. Accurate risk assessments of potential human exposures and support for decentralized laboratory capacity will be essential to ensure the most effective utilization of vaccines and RIG until canine rabies has been eliminated.

Contents

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1. Introduction

Almost all human rabies deaths worldwide result from dog bites. Most occur in Africa and Asia, where millions of exposures occur annually, and more than 50,000 people die each year as a result of the local unavailability of postexposure prophylaxis (PEP) with vaccine and rabies immune globulin (RIG) (Knobel et al., 2005). Even when these biologics are available, educational gaps or the absence of national recommendations may lead to their ineffective use (Folb and Cooke, 2007; Wilde, 2007).

Despite its global public health burden, canine rabies could potentially be eliminated from the human population in the next decades, since all of the necessary tools have been developed, validated and used in some form in specific parts of the world. Unfortunately, only rarely all tools have been used in programs implemented in coordination at the same time and at the same location. Achieving elimination will require governments, political leaders, local communities, international partners, subject-matter experts and non-governmental organizations (NGOs) to embrace a shared vision, commit to a long-term strategy and work together to implement existing prophylactic and control measures (Hampson et al., 2011; Lembo et al., 2011; Lembo and Partners for Rabies, 2012; Wilde et al., 2012). The prevention and control of emerging zoonoses requires cooperation among animal and human health sectors, ministries of education, local communities, international partners and NGOs (Arambulo, 2011; Batsukh et al., 2012; Wright et al., 2008). Success in eliminating canine rabies will therefore require a coordinated, integrated, interdisciplinary "One Health" approach (Briggs, 2012).

Creating a sustainable and successful rabies prevention program requires strategic planning and the carefully orchestrated spatiotemporal distribution of interventions for both humans and animals (Rupprecht and Slate, 2012). Extensive experience in industrialized countries and ongoing programs in Latin America, Africa, and Asia have demonstrated that the elimination of canine rabies is an achievable goal (Kamoltham et al., 2003a; Lembo et al., 2010; Schneider et al., 2011). All of these programs have had strong political support and have utilized a coordinated, evidence-based, community-oriented multidisciplinary approach. They have also avoided implementing one-sided strategies such as reliance on PEP without proper risk assessment, which is too costly and does not impact the source; indiscriminate dog culling without vaccination, which is unethical and ineffective; and canine vaccination without population management, which is unsustainable (Morters et al., 2012; Schneider et al., 2011; WHO, 2010).

2. Current opportunities and challenges for rabies elimination

2.1. Prevention of rabies in humans

In most countries where canine rabies is enzootic, control measures, supplies of vaccine and RIG, routine interventions, relevant recommendations and educational programs are either nonexistent or inoperative. The lack of effective educational outreach at the community level has led to gaps in knowledge as to the best way to avoid animal bites and administer first aid following bites or other potential rabies exposures. Inadequate education for veterinarians and physicians, insufficient resources for proper confirmatory diagnosis and risk assessment, and the lack of effective communication channels between ministries of health and agriculture frequently lead to failures of prophylactic intervention, even in regions where biologics are available.

Massive canine vaccination programs and widespread immunization of humans in the past few decades have significantly reduced the number of human rabies deaths in industrialized countries and many urbanized areas of developing countries (Fig. 1) (Hemachudha, 2005; Schneider et al., 2011; WHO, 2010). While both approaches are needed, the ratio of dog vaccination to human prophylaxis varies from country to country, and is largely based on the availability of biologics. Countries with higher gross domestic product or that produce their own effective vaccines are generally able to implement both approaches (Davlin and Vonville, 2012).

The most widely used biologics for human rabies prevention are cell-culture and chick- or duck-embryo vaccines, which are highly effective for pre-exposure prophylaxis (PrEP) or PEP, when used according to World Health Organization (WHO) recommendations (WHO, 2005, 2010). PrEP is recommended by WHO as well as ACIP (US Advisory Committee on Immunization Practices) for laboratorians, veterinarians and animal control personnel, as well as for people in remote regions who are at a high risk of rabies, but have limited access to PEP. PrEP currently consists of a 3-dose series of injections, that are most often administered intramuscularly (IM) on days 0, 7, and 21 or 28 (Manning et al., 2008; Rupprecht et al., 2010; WHO, 2010).

Three regimens are currently recommended for PEP following exposure to a rabid or potentially rabid animal (Table 1). The reduced, 4-dose Essen, Zagreb and ACIP regimens, used predominantly in Europe, the Americas, some African countries, Australia and the majority of Asian countries, are administered IM. The Thai Red Cross modified intradermal (ID) dose-sparing regimen is used on a regular basis in Thailand and the Philippines, and is slowly being introduced in India, Sri Lanka and other developing countries (Khawplod et al., 2007, 2012; Quiambao et al., 2005; Sudarshan et al., 2010, 2012; Warrell, 2012).

2.2. Prevention and control of canine rabies

Parenteral vaccination of dogs is the most effective method of preventing rabies in humans. Government- or NGO-sponsored mass vaccination campaigns, or the mandatory vaccination of owned dogs, has led to significant decreases in human rabies in many countries (Davlin and Vonville, 2012; Gongal and Wright, 2011; Kasempimolporn et al., 2008a; Schneider et al., 2007; Takayama, 2000). The WHO has recommended that a successful canine vaccination program should achieve at least 70% coverage (Davlin and Vonville, 2012; Kasempimolporn et al., 2008b; Schneider et al., 2007; Touihri et al., 2011). Given the high reproductive rates of dogs, their short life span and an age distribution that is often skewed towards a younger population in developing or impoverished countries, it is challenging to achieve effective long-term vaccination coverage (Davlin and Vonville, 2012; WHO, 2010).

Programs of canine rabies control often devote more energy to mass vaccination than to population management. However, some regions of India and Latin America have successfully used programs of spaying and neutering or animal birth control (ABC), combining surgical sterilization with rabies vaccination, to manage their dog populations (Totton et al., 2010). The ABC approach may be quite challenging and costly. According to some field studies and population demographic models, almost 90% of free-roaming dogs must be sterilized and vaccinated for vaccine coverage to remain above 70%, and to achieve a stable 70% reduction in the dog population within 13–18 years (Totton et al., 2010). Less than 40% surgical sterilization coverage would only maintain the dog population at its original level (Totton et al., 2010).

Another option for canine population management is chemical sterilization of male dogs, which has been used in Mexico, Brazil and other countries (Jana and Samanta, 2007; Oliveira et al., 2012; Soto et al., 2009). However, sterilization efforts should not focus only on males, as females are also critical target for effective population management (Fielding and Plumridge, 2005; Jackman

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