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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.

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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 have all the tools been used in programs implemented in coordination at the same time and 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., 2013; 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.

One health approach with 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 rabies 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 of canine population (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

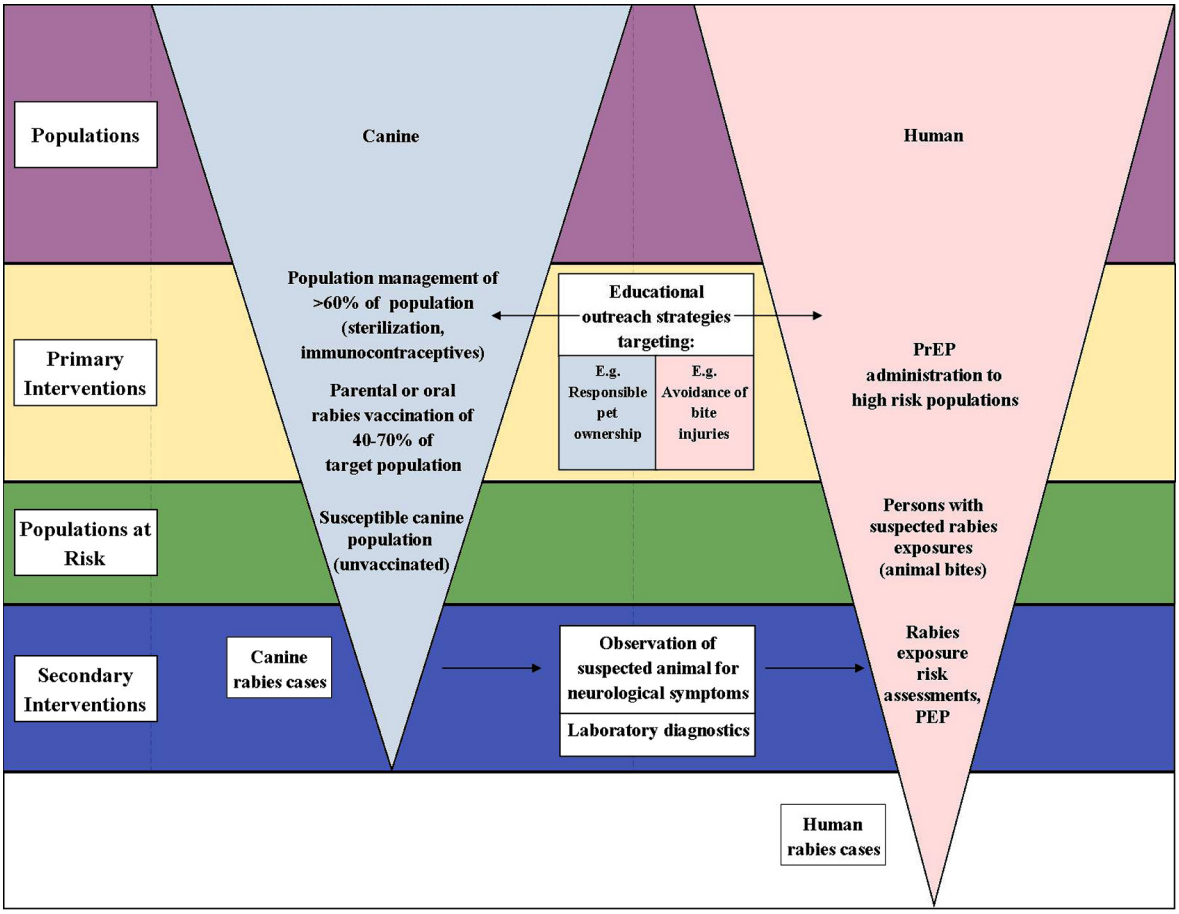

Fig. 1. One Health approach to canine rabies elimination (PrEP – pre-exposure prophylaxis, PEP – post-exposure prophylaxis). Implementation of various primary and secondary interventions lead to decrease in the number of people as well as dogs at the risk of rabies exposure and infection and ultimately to decrease in cases of animal and human rabies.

Table 1
Pre- and postexposure regimens for ID or IM vaccination currently recommended by the WHO[a] and the U.S. Advisory Committee on Immunization Practices[b] (Meslin and Briggs (2013)).

Vaccination	Number of doses of vaccine	Number of clinic visits required	Route of vaccine administration	Schedule of injections (days)
Pre-exposure				
Routine	3	3	ID[a] IM[a,b]	0, 7, 21 or 28
Post-exposure				
Essen	5	5	IM[a,b]	0, 3, 7, 14, 28
Zagreb	4	3	IM[a,b]	0 (2 doses in each deltoid) 7, 21
Reduced 4-dose	4	4	IM[b]	0, 3, 7, 14
Modified Thai Red Cross	8	5	ID[a]	(2 doses on each day) 0, 3, 7, 28
Post-exposure for previously vaccinated persons				
Two-dose	2	2	IM[a,b]	0, 3
Four-dose	4	1	ID[a]	(2 doses above each deltoid) 0

[a] Regimens recommended by WHO.
[b] Regimens recommended by ACIP.

population management (Fielding and Plumridge, 2005; Jackman and Rowan, 2010). More often, however, rabies control programs have attempted to cull dog populations, even though this approach has been shown to be ineffective (Dalla Villa et al., 2010; Johansen and Penrith, 2009; Morters et al., 2013; Rupprecht et al., 2006). Such lethal management strategies require the elimination of 50–80% of dogs a year, which is neither financially possible nor ethically acceptable (Rupprecht et al., 2002).

3. Future strategies for rabies prevention

3.1. Prevention of human rabies

As shown in Fig. 1, most cases of human rabies can be prevented by eliminating the disease in dogs, through a combination of Rupprecht et al. (2008), Wunner and Briggs (2010):

- appropriate risk-assessment programs, including laboratory confirmation or 10–14 day observation of animals causing a bite injuries or other potential exposures;
- evidence-driven selective administration of modern prophylactic tools;
- educational outreach; and
- sustainable programs of canine vaccination and population management.

Nevertheless, the lack of availability of rabies biologics in endemic countries has been a long-standing issue. The absence of data on the burden of rabies and the lack of education reaching the general public and health professionals on rabies prevention

measures have also contributed to the neglected status of the disease and the large number of potentially preventable deaths worldwide.

Political will is crucial for any sustainable disease prevention program. When there are many competing interests, gaining the attention of government will require accurate measurement of the disease burden, but because most endemic countries lack laboratory capacity as well as surveillance systems, their rabies burden has not been adequately quantified (Dodet et al., 2010; Knobel et al., 2005; Lembo et al., 2010). Efforts to eliminate rabies must begin by building laboratory capacity and quantifying disease rate, to permit the design of appropriate interventions and measure their impacts (Banyard et al., 2013).

Educational outreach and community engagement are critical requirements for successful rabies control programs, but they are often neglected (Dodet et al., 2008). Even though avoiding exposure to rabid animals is the most effective and inexpensive way to prevent human rabies, this strategy is often overlooked, and communities are frequently unaware of it. Breaking the vicious cycle of indifference and lack of information should be a priority of rabies prevention (Dodet et al., 2010). Given that most exposures and rabies cases are in children under 15, educational outreach at the family level is especially important (Hampson et al., 2008). Population surveys focusing on rabies prevention have repeatedly identified gaps in knowledge of risks, modes of transmission, avoidance of exposure and preventive measures (Altmann et al., 2009; Ichhpujani et al., 2006; Mai le et al., 2010; Matibag et al., 2007; Robertson et al., 2011). To build and strengthen health-promoting habits, effective rabies prevention requires changes in community health-seeking behaviors, including the avoidance of rabies exposures, immediate washing of bites with soap and water, and consultation with a public health professional after any animal bite.

Continuing education of physicians, veterinarians and other health professionals will ensure inter-sectoral coordination and communication on the local, national and international levels. By means of World Rabies Day events, the Global Alliance for Rabies Control (GARC) and other members of the Partners for Rabies Prevention (PRP) motivate and enable thousands of professionals and enthusiasts worldwide to educate people in their communities. GARC is reaching hundreds of thousands people annually with webinars and other electronic media (http://www.worldrabiesday.org/).

Successful rabies prevention programs rely on the engagement and empowerment of local communities (Kaare et al., 2009; Sintunawa et al., 2004). Implementation of lessons about the prevention of rabies and other zoonotic diseases in the school curriculum may significantly reduce dog bites and human rabies cases. This approach has been successfully implemented using the constructionist theory of experiential learning (“learning through play”), in which children do not just passively receive knowledge, but actively construct meaning (Agonnoude and Mesenge, 2010). The engagement of religious leaders and their communities is another effective approach. Provision of community leaders with culturally appropriate information, training, and promotion of skill-building activities may create a “ripple effect” of knowledge of rabies and its prevention as seen with other successful disease programs (Gore et al., 2012). Such educational outreach may decrease the number of rabies exposures, through avoidance of stray animals, and increase proper wound care by washing with soap and water, and through consultation and prophylaxis-seeking behavior. However, once a true exposure to a rabid animal has occurred, a modern cell-culture vaccine and RIG must be administered in accordance with WHO, ACIP or other national recommendations (Briggs, 2012; Rupprecht et al., 2010; WHO, 2010).

The pipeline for the development and production of new rabies biologics is decades long, and most rabies-endemic countries do not have local vaccine manufacturers, or have only a limited production capacity. Because human rabies vaccines are in the shortest supply in countries with the greatest need, new routes of administration, shortened schedules and dose-sparing regimens will need to be made available for communities in endemic countries. The Modified Thai Red Cross ID regimen is an ideal dose-sparing alternative to IM administration, which is recommended by the WHO and widely used in Thailand and the Philippines, and to a lesser extent in other Asian countries (Table 1). Because ID administration reduces the volume of vaccine required for PEP by as much as 80%, its use would be crucial where the vaccine supply is limited (Kamoltham et al., 2003b). However, because of its prolonged dosing schedule, the currently recommended ID regimen has sometimes led to poor compliance. A new one-week ID regimen (4-4-4, on day 0, 3 and 7) was therefore developed and is being evaluated in pilot studies in Thailand and India (Shantavasinkul et al., 2010; Sudarshan et al., 2012). Similar attempts to minimize the number of PrEP vaccine doses have also been initiated, and preliminary data suggest that a single full IM dose, or two 0.1 mL ID injections on one day, are adequate to prime immune memory and to obtain an accelerated immune response one year later (Khawplod et al., 2012).

Recent research on improved vaccine delivery has focused on the development and clinical evaluation of new devices for more reliable needle-free delivery, to reduce or eliminate needlestick injuries and the costs associated with their treatment. ID delivery devices such as microneedle patches are also being considered for future evaluation. Such patches may occupy less volume than vials or prefilled syringes, reducing demands on cold-chain capacity (Hickling et al., 2011). The inclusion of rabies PrEP in scheduled pediatric immunization for high-risk populations, when there are no better alternatives, is also garnering increased consideration (Lang et al., 2009; Shanbag et al., 2008). Multiple studies have demonstrated that the administration of PrEP to school-aged children is safe and feasible, and brings significant benefit to the community by providing long-term immunity and preventing deaths (Dodet et al., 2010).

Although human or equine rabies immune globulins (RIG) are an essential part of PEP, providing passive immunity until an immune response to vaccination has developed, they are frequently unavailable in resource-poor countries. A major barrier to wider access to these products is the need for human or animal plasma donors. New manufacturing practices and technologies to produce large quantities of “cocktails” of selected monoclonal antibodies may provide an alternative in the near future, expanding their availability throughout the world (Bakker et al., 2008; de Kruif et al., 2007; Gogtay et al., 2012; Goudsmit et al., 2006; Muller et al., 2009; Smith et al., 2011).

In addition to ensuring the availability of rabies biologics, there is also an urgent need to establish laboratory capacity and national risk assessment systems in regions where surveillance is limited or non-existent (Banyard et al., 2013; Briggs, 2012). Diagnostic and surveillance systems will provide the critical information to facilitate decision making regarding the need for PEP in cases of exposure to potentially rabid animals. Policy makers and health care professionals will also make use of reliable epidemiological data to design and implement the most appropriate and cost-efficient preventive measures for their situations (Fig. 1).

3.2. Prevention and control of canine rabies

The elimination of canine rabies is the most cost-effective long-term intervention to prevent the disease in humans. A combination of parenteral vaccination and population management of

free-ranging dogs, through surgical or chemical sterilization or capture and euthanasia, can successfully prevent rabies, provided the vaccination coverage approaches 70% and the dog population stabilizes or decreases (Lembo et al., 2012; Morters et al., 2013; Totton et al., 2010). Unfortunately, in many parts of the world, overpopulation is handled by culling, which is unethical and has only a transient impact (Jackman and Rowan, 2010; Morters et al., 2013).

Because of their intrinsic interconnections, public health, environmental protection and animal welfare are all improved by canine rabies vaccination and mass sterilization programs. The development of techniques to efficiently deliver rabies prevention and population control on a broad scale, with minimal technical requirements and low costs, is therefore imperative. Multiple single-injection methods for simplified population control in males, females or both genders are currently being evaluated. For example, Gonazon® is a contraceptive that contains the active substance azagly-nafarelin; if used as an implant in female or male dogs, it prevents gonadal function via long-term blockage of gonadotrophin synthesis (Goericke-Pesch et al., 2010; Ludwig et al., 2009).

GonaCon® (APHIS/USDA), a synthetic gonadotrophin-releasing hormone (GnRH) coupled to keyhole limpet hemocyanin and combined with a novel adjuvant, has been shown to suppress testosterone and estrogen production and reduce fertility in both genders in species such as deer and pigs, and induce high anti-GnRH antibodies in squirrels, rabbits, rodents, coyotes, horses, and bison, following a single dose (Killian et al., 2009; Miller et al., 2008). When GonaCon® was administered to dogs together with rabies vaccine, no interference with immune responses was observed (Bender et al., 2009).

Several studies have confirmed the efficacy of the GnRH peptide as an immunocontraceptive in both genders of various animal species. It has therefore been proposed that GnRH could be administered together with rabies vaccine in a dual immunocontraceptive vaccine, which would serve as a humane, ethical and highly efficacious means of both controlling dog populations and protecting against rabies (Wu et al., 2009). In preliminary experiments, three doses of the live or inactivated recombinant virus ERAg3p/2GnRH induced sufficient titers of anti-rabies antibodies and $\geqslant$80% level of immunocontraception in mice (Wu et al. unpublished data). If administered IM or orally in a mass vaccination campaign, such a vaccine would render animals of both genders both infertile and immune to rabies. However, one concern for acceptance of such a product is whether it is able to prevent estrus and its associated negative behavior, such as wandering and aggression among potential mates. The principal advantage of a dual rabies/immunocontraceptive vaccine is that it might be suitable for oral administration, allowing its administration via bait. By avoiding the need for animal capture, this would provide an enormous advantage for oral rabies vaccination and sterilization of free-ranging dog populations. Vaccines against GnRH would also have the advantage of suppressing sexual behavior in stray males and females (Kutzler and Wood, 2006).

Although novel approaches and more efficacious and accessible tools for rabies management are being developed and evaluated, proven tools are already abundantly available. If used wisely in coordinated, community-based, evidence-driven One Health approaches (Fig. 1), these tools will make possible the global elimination of canine rabies and the prevention of almost all human rabies deaths in the future.

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