

Research Article

Preventing Childhood Rabies Mortality in Asia

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Abstract

Rabies is a neglected tropical disease associated with almost universal mortality. It is most often caused by the rabies virus (RABV) and transmitted to humans through the bite of dogs, so-called 'canine' rabies. Approximately half of the considerable global burden of disease occurs in Asia where its burden falls most heavily on poor, rural populations with a disproportionate impact on children. The disease can be eliminated through control of the viral reservoir in dogs and there are examples of successful eradication in the region achieved through mass dog vaccination and dog population control. Rabies, however, is poorly controlled in other countries where advocacy is required to achieve political commitment and the establishment of dedicated rabies control programmes with strong inter-sectoral coordination and community collaboration. I briefly review the 2012 World Health Organisation South East-Asia region (WHO-SEARO) strategic control guidelines and consider specific actions and activities that will lead to a reduction in rabies deaths in Asian countries. In addition, by prioritising a goal to reduce child mortality in particular, I argue for the implementation of pre-exposure prophylaxis in children by administering rabies vaccines as part of the expanded programme for immunisation in the highest burden countries.

BACKGROUND

Rabies is a severe encephalitic illness caused by viruses of the genus *Lyssavirus*. The vast majority of cases globally are caused by the rabies virus (RABV or type 1 lyssavirus), which is transmitted to humans by the bite of canine species [1,2]. This so-called 'canine' or 'classical' rabies is described as "100% fatal but 100% preventable" [3].

Rabies is a neglected tropical disease associated with almost 60,000 deaths globally per annum, the highest number of deaths of any zoonotic disease, and this is likely an underestimation [1,2]. The overall burden of disease is considerable with an estimated 2 billion DALY's lost and an aggregated cost of US\$4 billion per annum [2] although the total cost may be even higher [2]. Figure (1) shows the global distribution of human rabies.

Approximately half of the global mortality occurs in Asia (45-59% or 23-39,00); [3,4] 1.4 billion people remain at potential risk in the South-East Asian region alone [3,6]. In Asia, the economic cost of rabies is primarily that associated with the use of vaccines and immunoglobulin as post-exposure prophylaxis (PEP) in humans, the use of which is increasing [6-8]. Rabies has been successfully eradicated in some countries in Asia through dog vaccination and dog population control including: Japan, Singapore, Malaysia, Taiwan, Hong Kong, and South Korea [4]. Furthermore, a significant reduction in the incidence of disease

has been achieved in Thailand, Sri Lanka and Vietnam through mass dog vaccination, expanded use of PEP in humans and education campaigns [3,4]. Rabies has been controlled using the same approach in the Americas [5]. Despite these successes, the incidence remains unchanged in many countries, with particularly high rates in India, Myanmar (Burma) and Bangladesh. A striking figure that illustrates the current state of control in the South-East Asia region is that only 20% of cases of dog bite receive appropriate and timely PEP [6].

EPIDEMIOLOGY AND DETERMINANTS OF HEALTH

Studies of canine rabies cases show that it primarily affects rural populations and the urban poor [3,4,9,10]. A high proportion (40-50%) occurs in children, [9,10] and the overall underestimation of rabies incidence may also particularly apply to childhood cases [8]. It is thought that a significant number of deaths occur without prior presentation to health care services, and that there may be a reporting bias with encephalopathy in children often attributed to other causes [3,6]. Furthermore, rabies cases are associated with delayed, or lack of, presentation for PEP often because individuals are ignorant of the need, or PEP services were not readily available [6].

Studies of dog bite epidemiology have further elucidated factors associated with dog bite risk and delay in initiation of

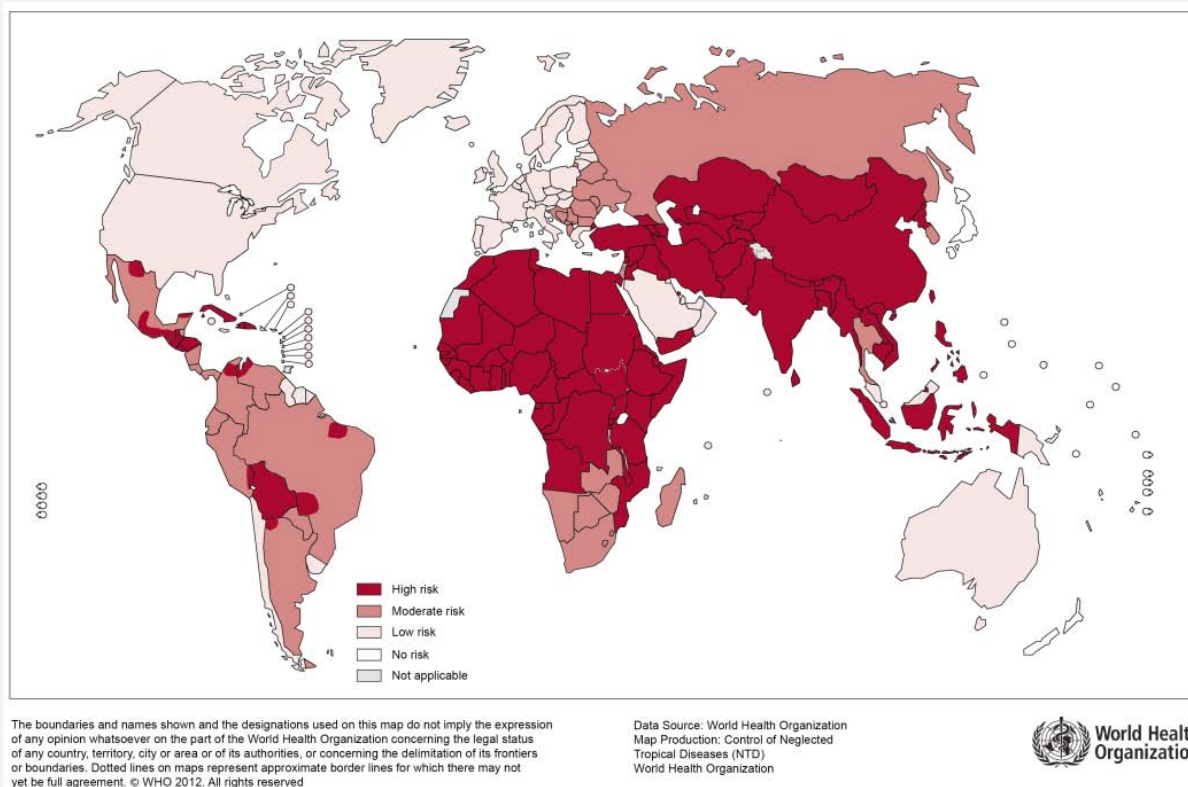


Figure 1 Global map showing the distribution of risk levels for humans contracting rabies, 2011. (Sourced from reference 10).

PEP, both important determinants of rabies deaths. A multicenter study of bites presenting to anti-rabies centers (ARC) in India [12] showed that 47.5% of bites occurred in children 2-18 years old and 72.4% of bite victims were male. There was evidence of an education gap; in only 58.5% of cases had the wound been washed with soap and water, and 1 in 10 cases had applied traditional cultural remedies or presented to traditional healers prior to presentation to the ARC [13]. Studies have shown that bites frequently go unreported in children; that children are at increased risk compared with adults; and that bites in children are more often on the face and head, which is associated with a more rapid progression of disease [6]. Another study from an urban hospital in India [13] showed that two thirds of dog bite cases were male; two thirds from rural areas, and one third were illiterate. Delayed presentation was associated with increased distance from an ARC, a lower family income, an unawareness of the need for timely PEP, and the ARC being closed [13]. Studies from other locations have emphasized this lack of public awareness about dog bite care and PEP and the prevalence of traditional beliefs/practices as a barrier effective treatment [4,6]. The rural-urban gradient in the epidemiology of rabies represents a combination of these factors [4]. Furthermore, in countries with active control efforts focused on prevention of disease in the dog population, these activities often do not extend beyond urban locations because of cost and acceptability of programs to the community [6].

PUBLIC HEALTH RESPONSE

An analysis of those countries in Asia in which successful

control of rabies has been achieved has served to highlight the following elements as important to success [4] a dedicated rabies control program, effective surveillance in which rabies is made a notifiable disease, a strong regulatory and legislative framework, a list of defined goals for incidence reduction, active control of the animal reservoir, PEP made widely and freely available, a move to intra-dermal as opposed to intra-muscular administration of PEP with associated cost reduction and public education programmes. It is worth noting that the application of different combinations of these elements in Thailand and Sri Lanka when compared to Singapore and Malaysia has been associated with success, pointing to some degree in flexibility of approach [6]. This is critical given the differences in disease burden, financial and technical capacity and socio-cultural factors across the region. It does however appear that, in terms of achieving elimination, that mass dog vaccination is essential [1,6]. This poses a major challenge because of cost [5]. Another costly aspect of rabies control activities is intensified PEP, in particular that associated with the complete phasing out of the production and use of nerve tissue vaccines (NTV's) in humans and move to more effective tissue culture vaccines (TCV's) and the availability of immunoglobulin [3,4,6].

In addition to the financial costs, other barriers to control include: a lack of high level political commitment; a lack of coordination and leadership across sectors; inadequate and insensitive disease surveillance systems; limited accessibility to modern vaccines; and poor community education, engagement and cooperation [4].

A major factor contributing to poor control that was identified in regional consultations was a lack of consensus at a national level as to the best approach to apply. In response to this, the WHO office of the South-East Asia region (SEARO) has developed a *Strategic Framework for Elimination of Human Rabies Transmitted by Dogs in the South-East Asia Region* [8]. The three core elements of the framework are the prevention of animal rabies, better public awareness and improved access to human rabies vaccines [8]. These elements are further elucidated in the guiding principles in this document: that human rabies prevention is possible through mass dog vaccination, promotion of responsible dog ownership and dog population control programs; that dog bite wound management is an important step which needs to be promoted at the community level through advocacy, awareness and education; and that PEP should be easily accessible, affordable and available for those that require it [8].

Number of key activities are required in order to apply the framework at a national level [3,6]. From a policy perspective, countries need to develop a comprehensive national rabies control program. Central to the operation of such a program is the coordination of the activities of the three key government bodies already involved in rabies control activities in most Asian countries: the ministries of health, agriculture and local governments. Given that the main vision of the program is the elimination of human deaths from rabies, situating the program primarily under the responsibility of the national ministry of Health is most appropriate. Such a program will require the appointment of program officers and potentially the establishment of specific statutory bodies or the passing of specific legislation, as has occurred in Thailand and the Philippines [4]. Where applicable, the program must negotiate a phase out of NTV's and promote the use of the cost-effective intra-dermal delivery of vaccines [6]. This will require the re-drafting of health policies and guidelines as well as the securing of international supply chains and in-country logistics. Important facilitators of scaling up PEP across the region are that India is now capable of producing enough TCV for the SEARO region (estimated 15 million doses), and that equine rabies immunoglobulin (RIG), which is cheaper than human RIG, is now better purified to improve safety [6].

In terms of prevention of animal rabies, the ministry of agriculture and veterinary services are required to develop regulatory frameworks for dog registration and animal movement/transfer and mechanisms for the delivery of dog vaccination [3]. Other elements of dog population control may include active sterilization of stray dogs or euthanasia of stray dogs, although this may be unacceptable in certain cultures.

The establishment of such a program represents a significant leadership challenge in many countries. It will involve advocacy at the highest levels of government to achieve national commitment. Once such a commitment is achieved, the need for the establishment of agreed targets (both operational, and outcome targets) is essential [8]. Given the necessity of inter-sectoral coordination and collaboration, effective leadership is required to establish a shared agenda and goals. The activities of a national rabies program will also likely require international

partnership with WHO and non-government organisations for funding and implementation, such that a strong national vision is required to achieve the most effective local implementation of regional strategies. Clear communication between the many actors will be foundational to success. A further communication challenge is the need for extensive community engagement throughout [3].

From a public health perspective, two key areas of activity need to be established [3,8]. The first is effective disease surveillance. The second is health promotion. To achieve effective rabies surveillance, the disease must be made notifiable, and both ante-mortem and post-mortem diagnostic capacity in humans and animals needs to be established at a national and sub-national level, with clear processes for data collection and reporting. Authenticated data on rabies cases should be regularly collated and ideally be made publically available. This will improve the validity of regional/global disease burden estimates and enable monitoring of trends; a critical tool for evaluating the success of control efforts. In terms of health promotion activities, community engagement and health education campaigns with a particular focus on dog bite management and responsible dog ownership are the top priorities. Additionally, existing health services may need to be made capable of delivering PEP as close as possible to communities.

Given the proportion of dog bites associated with stray or unowned dogs, dog population control is important. An important ethical consideration in many contexts is what initiatives will be acceptable to the community. There is international consensus that there must be maintenance of appropriate animal welfare in the implementation of dog eradication practices [6]. Furthermore, it is likely that the cost of animal vaccination is cheaper than animal elimination [4]. A second important ethical consideration that forms the basis of the advocacy for a response to NTD's generally is the importance of equity. National programmes should be particularly encouraged to address the urban-rural gradient in the access to PEP including immunoglobulin [2].

One element of a possible public health response that remains inadequately addressed is the use of pre-exposure prophylaxis (PrEP) in the form of vaccination in high-risk populations, particularly children. Given the global agenda to reduce childhood mortality, this approach deserves further consideration. The WHO position paper on the use of rabies vaccines [1] encourages further studies of incorporating cell culture vaccines into childhood immunization programs, but not its implementation. The possibility of including rabies vaccine in the expanded program of immunization (EPI) has been suggested, although in a recent review article [2] the cost-effectiveness of such an approach with current vaccines was described as "questionable" [2]. However, there is data to show that rabies vaccines given to children produces sustained immune responses and that this is not effected by them being co-administered with other vaccines contained within the EPI [14,15]. A modeling study of the cost-effectiveness of rabies PrEP in children from Thailand [16] showed that cost equivalence can be reached between intradermal PrEP (vaccine without RIG inclusive of PEP without HRIG following dog bite) and intramuscular PEP with HRIG at a dog bite prevalence of only 2%. This data would support the

use of childhood PrEP, if administered in regions with a high prevalence of dog bites and high rabies risk. In Asia, the countries with highest prevalence (e.g. Bangladesh and Myanmar) where dog rabies prevention is yet to be widely implemented effectively constitute the locations where implementation of this approach should be considered. This strategy would not obviate the need for rabies control in the dog population, but should be considered as a temporary measure until dog control measures are implemented effectively. Given that these countries have established systems and workforce to effectively administer the existing EPI [17,18] scale-up of childhood PrEP is likely achievable. There is a need for trial implementation of such an approach to generate much needed evidence for the effectiveness of childhood PrEP, its feasibility and costs.

CONCLUSION

Rabies can be effectively controlled, if not eliminated in Asia. A particular short term goal should be that of reducing childhood mortality from rabies. This could be achieved through the application of the WHO regional strategic framework with the additional targeted introduction of rabies immunisation into the EPI in countries with highest rabies incidence.

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