

REVIEW ARTICLE

A review of current strategy for rabies prevention and control in the developing world

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Abstract

The control of Rabies, a zoonotic viral disease is a major public challenge in several developing countries. Current approaches for rabies control are overwhelmingly directed towards provision of effective post exposure prophylaxis (PEP) to animal bite victims. The enormous costs involved in rabies prophylaxis is an important factor precluding its universal application in all animal bite victims especially in those residing in resource constrained settings. The intradermal route of administration has been shown to be cost effective except in peripheral regions with fewer animal bite cases. Nevertheless, rabies control program with their expected emphasis on human rabies prophylaxis have neglected canine vaccination. The feasibility of canine rabies vaccination depends primarily upon allocation of resources through political commitment and effective public private partnerships. However, in large parts of the world including India formal dog ownership constitutes a small minority of the overall canine population while state funded canine vaccination drives often fail to impress policy makers who struggle to maintain budgets for adequate coverage of rabies PEP for animal bite victims. The key to rabies control may therefore rest upon a one health approach with development of newer vaccine technology which is cost effective for vaccination in both, man and animal.

Keywords

Rabies; India; Vaccination; Prevention

Introduction

Rabies is zoonotic disease of immense public health importance. It is a viral disease of the Central Nervous System which causes encephalomyelitis and is 100% fatal in absence of effective post exposure prophylaxis (PEP). The rabies virus is spread to humans from animal bites since the virus is excreted in the saliva of the diseased animals. In developing countries, dogs are the predominant reservoir of

infection (canine rabies) while other animals like bats, racoons and foxes are principle reservoirs of infection (sylvatic rabies) in developed countries (1). Rabies is a neglected tropical disease and its highest burden is experienced in some of the poorest regions of Asia and Africa where the disease prevalence is uniform across territories and of a stable pattern (1). Asia has the highest burden of human mortality due to endemic canine rabies with South Asia containing the maximum population at risk of infection (2-3).

The maximum incidence of Rabies has been reported from India with over 20,000 deaths per year (3). The disease burden estimate in the developing world is considered to be an underestimation as per the World Health Organization (WHO) because of factors like poor surveillance and underreporting, frequent misdiagnosis of rabies and an absence of intersectoral coordination (4). Furthermore, it is particularly problematic among rural poor due to lack of effective management with PEP following dog bites in them arising from ignorance, illiteracy, lack of availability and accessibility to affordable rabies PEP services (4-5). Rabies particularly affects children aged 5-14 years especially males due to their propensity for greater contact with canines and who thereby constitute almost 40% of the rabies PEP recipients (6).

The cost of human rabies is estimated by the World Health Organization (WHO) to be close to 1.9 million DALYs due to mortality and morbidity arising adverse effects following vaccination, pain during vaccination and mental trauma on being bitten by a suspected rabid animal (6). Furthermore, there are considerable economic costs associated with PEP both for the patients due to the out of pocket expenditure, loss of wages and travelling costs during management and the (government) health facilities which need to invest resources to procure sufficient Anti Rabies Vaccine (ARV) and rabies immunoglobulins (RIG), training of personnel involved in vaccination and associated opportunity costs for maintaining continued PEP in the population.

Treatment of dog bite victims in rabies endemic countries like India needs to be initiated immediately since all animal bites are considered from suspected rabid animals (1). The appropriate post exposure management includes an initial local management of animal bite wound through effective wound toilet and application of antiseptics to destroy the outer coating of the rabies virus (1). Tetanus toxoid is provided to known or suspected un-immunized individuals. Suturing of wound is suggested to be delayed by 24-48 hours unless necessitated by its depth, tearing of flesh or incessant bleeding. Suturing when necessary should be preceded by the local application of RIG in the wound (7).

Local management should be followed by provision of both passive and active immunization to induce production of protective antibodies and inactivation of the rabies virus (1,6).

VACCINATION GUIDELINES IN RABIES POST EXPOSURE PROPHYLAXIS

Post exposure treatment in animal bite management is classified into 3 categories as per the National guidelines for rabies prophylaxis in India (Table 1) [7]. The WHO guidelines for rabies prophylaxis instruct animal bite cases who present for evaluation and rabies post-exposure prophylaxis even months after percutaneous exposure from a suspected rabid animal should undergo the same treatment as an animal bite victim with history of recent contact due to the long incubation period of the disease (8).

Anti-Rabies Vaccines (ARV) constitute the cornerstone of rabies PEP and India has significantly expanded its production of ARV in the last two decades (Table 2). Multiple ARV regimen exists for rabies PEP which vary primarily depending upon the route of administration of the vaccine (Table 3).

The application of Antirabies serum (ARS) is recommended in category III exposures following animal bites in the depth and around the wound since the rabies immunoglobulin has the property of binding with the rabies virus resulting in its inactivation (6-7). ARS is available as of human (HRIG) and equine origin (ERIG). HRIG is associated with minor side effects like transient tenderness at injection site. However, ERIG may be associated with anaphylactic shock and hence may be preceded by a skin test to determine sensitivity to ARS. Preparation for the management of potential anaphylactic shock irrespective of the result of the skin test should be available prior to any ARS application. The dose of ERIG is 40 I.U per kg body weight of the patient with a maximum dose up to 3000 I.U while the dose for HRIG is 20 I.U per kg body weight of the patient with a maximum permissible dose limit of 1500 I.U beyond which there is a potential decrease in its protective efficacy (7-8).

In absence of availability of ARS at the time of initiation of PEP with Anti Rabies Vaccine, the wound toilet should be performed with greater conscientiousness in order to reduce chances of the virus survival. Furthermore, ARS may be provided to an animal bite patient already initiated with ARV for a period extending up to the 7th day from day of bite beyond which it is not indicated since it could interfere with the antibody response generated by the ARV. ARS application in individuals who have received it during any previous animal bite exposure in their lifetime is unwarranted (7-8).

The WHO no longer recommends nerve tissue vaccines despite their lower production costs due to their association with significant adverse effects especially neuromuscular reactions, decreased immunogenicity and long duration of treatment with ≥ 10 -14 injections required for production of effective antibody response (2). The use of nerve tissue vaccines has been abandoned in all countries globally except Mongolia, Myanmar and Pakistan (4). Cell culture vaccines have supplanted neural tissue vaccines in India. Adverse effects following immunization with cell culture vaccines is low and they are usually well tolerated (9). These vaccines should be kept and transported at temperatures between 2-8 degree Celsius. There is no known contraindication to rabies vaccination and it is permitted in pregnant women and among immunocompromised populations (6-8).

The routes and dose of administration of WHO approved Anti Rabies include [8]:

(a) Intramuscular injection: Usually single injection is given in any of the deltoid. Dose is 0.5 or 1 ml depending upon the vaccine type and manufacturer.

(b) Intradermal injection: The dose of the vaccine in volume per intradermal site is 0.1 mL for both PVRV and PCECV. One dose of vaccine, in a volume of 0.1 ml is given intradermally at two different lymphatic drainage sites (bilaterally), usually on the left and right upper arm. WHO guidelines state that the vaccine administered intradermally must raise a visible and palpable "bleb" in the skin and if a dose of the vaccine is erroneously given subcutaneously or intramuscularly, a new dose should be administered intradermally. The cases with previous history of receiving complete rabies PEP course should be provided two booster doses of ARV on Day 0 and 3. However, immunocompromised cases like HIV/AIDS patients should be given complete 4 dose PEP.

Pre-exposure prophylaxis: is recommended in those persons who are at high risk of exposure to live rabies virus like laboratory staff, veterinarians, animal handlers and wildlife officers (8). Furthermore, If the suspected animal is noted to be alive and healthy after an observation period of 10 days, the post exposure prophylaxis vaccination may be converted into a pre-exposure prophylaxis regimen (10).

BARRIERS TO UNIVERSAL PEP VACCINATION IN ANIMAL BITE VICTIMS

Rabies is 100% fatal but it is also completely preventable with application of existing vaccination technology. Rabies could potentially be eliminated from the human population due to availability of efficacious vaccination tools which have been validated across the world. The challenge of eliminating global rabies should preferably adhere to a 2-pronged strategy which combine goals for prevention of rabies in humans with effective PEP and prevention and control of canine rabies by parenteral vaccination of dogs to interrupt the chain of transmission (10). Nevertheless, few countries in the developing world are rabies free while nearly all deaths due to rabies occurs in the developing world and according to WHO estimates the annual cost of rabies may be in excess of US \$6 billion per year which strains their limited public health budgets (4). The WHO technical report citing the internal market data of (anti rabies) vaccine manufacturers suggest that at the global level, ≥ 15 million people receive rabies prophylaxis annually, the majority of whom live in China and India with the Asian cost for PEP estimated to be \$1.5 billion annually (4). Despite the enormous investments made by the public health systems in several developing nations including India for preventing rabies fatalities in humans by expansion of PEP facilities, the high rabies burden persists albeit with decreased mortality due to the disease (4).

Unfortunately, there exist several barriers and challenges to universalization of rabies PEP in the resource constrained healthcare settings of the developing world.

(a) Lack of community knowledge of effective appropriate post exposure prophylaxis in dog bite management especially in rural, marginalized and low socioeconomic status households and poor neighbourhoods in cities where incidentally human and animal (dog) interaction is maximum poses a threat to universal adoption of PEP for rabies prevention (4, 11). Several surveys have shown that such vulnerable population often employ undesirable practices like application of irritants like chilly powder at the site of animal bites (11).

(b) Despite the provision of free of cost rabies PEP in government run health care centers across India, segments of population in remote areas may miss out on PEP due to problems of accessibility or

irregular functioning of health centers often due to administrative lacunae and logistical limitations. Other vulnerable populations include dog bite victims who are daily wage earners who report delay in initiation or fail to adhere to rabies PEP regimen due to requirement of multiple visits and long distance from the treatment facility (11-12).

(c) Medical doctors and residents may possess inadequate levels of knowledge for appropriate rabies PEP management (15-16). This may be associated with vaccine wastage during management of those incident animal bite cases reporting both history of previous suspected rabid animal bite followed by a complete course of recommended PEP with ARV with or without ARS. This is even more likely when the animal victims are of low educational status and furnish the relevant history in a manner which is interpreted as unreliable by the treating physician who often in such situations confronted with the possible risk of rabies fatality provide a complete course of new PEP with four doses instead of two in violation of standard rabies prophylaxis guidelines (17).

(d) Rabies prophylaxis is an emergency and a lifesaving prophylaxis but its adoption also places enormous burden on national economies in the developing world. The market rates of rabies PEP costs more than the average monthly wage in most South Asian countries. Hence, governments in low income countries need to heavily subsidize and often provide complete free services for rabies PEP to protect their poor for whom the out of pocket costs for animal bite management especially vaccination costs are economically catastrophic and unaffordable. Despite these vast governmental initiatives, only an estimated 1.8 million people receive rabies PEP in India while accounts for only half of the incident animal bite cases in the country (4). Health budgets will need to be considerably enhanced in order to achieve universal PEP for most incident animal bite cases in developing nations.

STRATEGIES TO COMBAT RABIES IN THE DEVELOPING WORLD

The increased thrust on provision of PEP in the developing world has invariably neglected prioritization of canine rabies control programs (4). Primary prevention of rabies requires vaccination of dogs as an essential prerequisite for virus management in animal populations by building sustainable herd immunity in dogs through a 'one

health' approach (11, 18). Epidemiological data from several Asian and African nations suggest that Annual mass vaccination campaigns are the most effective means to control canine rabies (19).

Improving vaccination in canines requires sustained political commitment through such investment which prioritizing rabies control in dogs such that canine vaccination levels are accepted as a critical indicator of the rabies control program. Unfortunately, there is global lack of consensus on the ethical, technological and economic feasibility of a rabies program which radically reorients, if not diverts limited healthcare resources towards vaccination of dogs instead of augmenting PEP care in humans. Moreover, the costs involved in canine vaccination where found in a study by Abbas *et al* (2014) in Chennai, India to be almost 3-10 higher than costs for providing rabies PEP which renders it difficult for stakeholders to challenge the overwhelmingly emphasis on the latter in existing policy (19). There are other sociological challenges towards increase vaccination coverage in dogs in India since most dogs in India are not formally owned by humans unlike developed nations and even Africa where almost 98% of dogs are owned and accessible (20).

Furthermore, building strategic and sustainable partnerships between the government agencies for human health and animal welfare with non-governmental agencies involved in delivery of services to increase knowledge and promote positive dog bite management practices in vulnerable human population or societies helping with vaccination of stray canines, enhancing rabies surveillance and developing multiple reference laboratories for early diagnosis of rabies are indispensable for long term rabies control (21-22).

Governments could focus on reduction in dog bite incidence by reducing stray animal population by sterilization for birth control, improving knowledge in populations and reduction of undesirable human animal interaction. However, the elimination mass culling of dogs is ethically subversive and scientifically proven to be ineffective in rabies control and hence should be strictly avoided (24). Moreover, the majority of the population in developing nations like India and Sri Lanka are likely to be averse to such violent initiatives due to their religious beliefs (25).

The strategies for reduction in the enormous costs involved in rabies PEP should also be explored. The

use of intradermal vaccination for rabies PEP is expected to reduce the volume of vaccine required as compared to intramuscular injections by 60-80% while being safe and immunogenic (6, 26). However, the application of vaccine by intradermal route requires specialized and trained health personnel who might be unavailable in rural areas. The cost effectiveness of the intradermal route is also lost in peripheral health facilities with fewer dog bite cases per week multi use vaccine vials are often discarded while incompletely used (27).

Abbreviated intradermal regimens requiring fewer injections and visits as alternative in place of current WHO approved regimens could dramatically reduce the cost of vaccination but their efficacy and immunogenic response have yet to be sufficiently validated in reference populations (28).

Measures to contain ARV wastage through excess vaccination in previously vaccinated animal bite cases should also be considered by defining algorithmic mechanisms when the healthcare provider is confronted with unreliable patient histories or lack of past medical records (17).

In conclusion, Rabies control and elimination while theoretically feasible with existing scientific and technical tools is hampered by the exponential and unsustainable costs required for their universal application especially in the global south where the disease is most prevalent. The key to rabies control may therefore depend upon development of newer rabies vaccination technology which is cost effective for vaccination in both, man and animal. Furthermore, current program efforts for rabies control and elimination should be focused upon efficient vaccination strategies and reducing vaccine wastage for improving cost effectiveness of rabies PEP. Targeting enhanced healthcare seeking behaviour through appropriate IEC activities and improving vaccine access in vulnerable populations is also necessary to enhance rabies PEP coverage and prevent avoidable rabies cases.

Recommendation

Community mobilization and advocacy with health partners to generate political commitment for ensuring universal uninterrupted PEP services especially in rural settings.

Regular training of healthcare providers involved in treating animal bite victims to ensure correct PEP prescription as per recommended guidelines. Rabies control policy should promote a 2-pronged strategy

which combine goals for prevention of rabies in humans with effective PEP and prevention and control of canine rabies by parenteral vaccination of dogs to interrupt the chain of transmission especially in regions with high animal bite injury burden and greater population density.

Authors Contribution

SG contributed to concept, design, manuscript editing, manuscript review. SB and ND contributed to design, literature search, analysis and manuscript preparation.

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Tables

TABLE 1 POST EXPOSURE TREATMENT IN ANIMAL BITE MANAGEMENT IS CLASSIFIED INTO THE FOLLOWING CATEGORIES AS PER THE NATIONAL GUIDELINES FOR RABIES PROPHYLAXIS IN INDIA [7]

Category	Type of contact	Type of exposure	Management
I	Touching or feeding of animals Licks on intact skin	None	None, if reliable history is available
II	Nibbling of uncovered skin Minor scratches or abrasions without bleeding	Minor	Wound management Anti rabies vaccine
III	i. Single or multiple transdermal bites or scratches ii. Licks on broken skin iii. Contamination of mucous membrane with saliva	Severe	Wound management Rabies immunoglobulins Anti rabies vaccine

TABLE 2 ANTI-RABIES VACCINES (ARV) AVAILABLE IN INDIA [ADAPTED FROM REF. 1]:

Name of the vaccine	Fixed virus strain	Substrate	Availability in India
1. Neural tissue vaccine (Semple type) BPL inactivated sheep brain vaccine	PV – II	Sheep brain	Production stopped in Dec' 2004
2. Cell Culture Vaccines			
(i) Human Diploid Cell Vaccine (HDCV)	Pitman Moore	MRC-5	Imported
(ii) Purified Chick Embryo Cell Vaccine (PCEC)	LEP-Flury (Rabipur) Pitman Moore	Primary SPF	Private sector
(iii) Purified Vero Cell Rabies Vaccine (PVRV)	(Indirab)	Vero cells	Public/Private sector
3. Purified Duck Embryo Vaccine	Pitman Moore	Duck embryo	Imported

TABLE 3 THE FOLLOWING ARV SCHEDULES USING CELL CULTURE VACCINES ARE RECOMMENDED AS PER WHO GUIDELINES [7]:

Type of prophylaxis	Route	Schedule	Number of visits
I. Post exposure prophylaxis			
(i) Essen regimen	Intramuscular (IM)	0,3,7,14,28*	5
(ii) Zagreb regimen	Intramuscular (IM)	0**, 7, 21	3
(iii) Thai red cross regimen	Intradermal (ID)	0, 3, 7, 28 (2-2-2-0-2)	4
II. Pre exposure prophylaxis	IM / ID	0, 7, 28	3
III. Post exposure prophylaxis of previously vaccinated***			
(i) Two visit	IM / ID	0, 3	2
(ii) Single visit (Four doses)	ID	0	1

* A Day 90 or 6th dose may be provided to those individuals who are immunocompromised, at extreme ages or on steroid therapy.

** Two doses are given on day 0 in each of the deltoid

*** Those who have received full course of rabies PEP with cell culture vaccines need to be only provided two booster doses of ARV on Day 0 and 3. However, immunocompromised cases like HIV/AIDS patients should be given complete PEP consisting of four doses.