SPECIAL ARTICLE

Improving Vaccination coverage of Humans as well as Dogs – Two important steps towards Elimination of Rabies

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Rabies is being targeted for elimination from India by 2030. It requires combined efforts of government agencies, medical and veterinary professionals, private and non-government organizations as well as industry bodies involved with manufacture and supply of biologicals used for prevention of Rabies both in humans as well as carrier animals. Vaccination of host animals is as important as timely prophylaxis of humans to get rid of the disease as rabid animals can keep infecting humans unless they are disease free. Human Biologicals Institute (HBI) has been playing a key role since its launch in 2000 by supplying increasing volume of modern purified vero cell cultured anti-rabies vaccine Abhayrab® from its facility at Udhagamandalam, Tamil Nadu, for vaccination of humans and has commenced supply from its new facility at Karkapatla, Telangana. Its parent organization Indian Immunologicals Limited has been contributing to the effort since 1989 by consistently supplying modern BHK cell cultured anti-rabies vaccine Raksharab for vaccination of animals from its facility at Hyderabad.

Rabies is a viral zoonotic disease which causes significant number of mortality in humans, especially in impoverished countries. Rabies virus (RABV) can have different reservoir host species of mammals. The most important of these reservoirs as a source of human disease is the domestic dog. Transmission of RABV most commonly occurs following a bite from an infected host resulting in the deposition of virus-laden saliva into the wound. RABV is highly neurotropic and after a highly variable period, from a few weeks to months, it gets into peripheral nerve and travels to the dorsal root ganglion. Once within the spinal cord, the virus ascends to the brain, resulting in encephalitis that manifests in clinical signs and symptoms that can be categorized as either furious type or paralytic type of rabies. The more common and classical form furious rabies is characterized by symptoms of hydrophobia (fear of swallowing), aerophobia (fear of air current), and aggressive behavior. The paralytic form, also known as silent rabies, presents with ascending flaccid paralysis and in most cases, without the classical symptoms of hydrophobia or aerophobia. While the furious form mostly results in death within one week, in silent/ paralytic form of rabies the patient survives for weeks before ultimately succumbing to paralysis of respiratory muscles [1,2].

Across the world, canine rabies kills tens of thousands of people every year despite being a disease that is preventable by timely and proper prophylaxis. Repeated and well planned efforts of mass animal vaccination had led to the elimination of spread of rabies by domestic

dogs in high-income countries. Rabies now remains as a disease mostly in low and middle-income countries in Asia and Africa, and common among people living in rural, underserved populations where dog vaccination is rare. Following a rabid dog bite, prompt post-exposure prophylaxis (PEP) is the only way to ensure that the invariably fatal onset of rabies is prevented. Statistical modeling suggests that unless efforts for dog vaccination are scaled up and gross improvements made in the PEP access, over 1 million people are likely to die of dog mediated rabies

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between 2020 and 2035 [3].

Anti-rabies vaccine (ARV) is the most important component of PEP against rabies. In India, ESSEN regimen (comprising of five doses, one each on days 0,3,7,14 and 28) has been approved for intramuscular administration while Modified Thai Red Cross regimen (intradermal administration on 2 sites each on days 0,3,7 and 28) is the approved schedule for intradermal administration. A rabies virus neutralizing antibody (RVNA) titer of ≥0.5 IU/ml on day 14 after completion of vaccination with ARV is the consensus surrogate parameter agreed upon globally as indicative of an adequate response to immunization. Rabies vaccines can be administered by the intra-dermal (ID) or intramuscular (IM) route and various schedules have been approved in different countries. Intra-dermal rabies vaccination was promoted by the World Health Organization (WHO) since 1992 after it was recommended by an expert committee constituted by it in 1991. This alternate route of administration has been shown to reduce the cost and dose requirement of vaccine by 60–80%, especially when used at high-volume clinics manned with trained staff. In the world, it was first used in Thailand in 1990 and introduced in India after WHO recommendation around 2006 [4,5,6, and 7].

Though ID regimens could cut down the cost, due to the long duration of the schedules, persons requiring PEP often would not complete the full course of vaccination. The high cost of rabies PEP and likelihood of loss of income due to time spent in frequent travel to the clinic also pose as further barriers to treatment, particularly in lower-income countries where rabies is common. Available evidence supported feasibility of having PEP schedules with reduced duration, and in some cases, also reduction in number of doses administered without significantly affecting immunogenicity and effectiveness against rabies. Evidence in favor of the 1-week 2-site ID regimen was recently supported by good clinical effectiveness and immunogenicity data from Cambodia, a rabies-endemic country. Reducing the number of visits and the associated costs by using these abridged regimens is likely to improve patient compliance. Based on these, the 2018 update of the WHO position on rabies vaccines addressed the need for more programmatically feasible recommendations that can improve overall outcomes for rabies while maintaining the efficacy at individual level. The update considered the most recent evidence available to improve access to PEP to meet the needs of underserved populations better through shorter, less costly and more feasible schedules. These new PEP schedules for immunologically naïve individuals (of all age groups) include (a) 2-site ID administration on days 0,3 and 7 or (b) 1-site IM administration on days 0,3,7 and a final dose between days 14–28 [6,8, 9].

A multi-centric trial proposed by APCRI to evaluate the newly proposed abridged ARV administration schedule is a welcome step which will help in establishing whether these schedules can be followed in countries like India. In this schedule known as one week Institute Pasteur, Cambodia regimen (2-2-2-0-0), intra-dermal doses will be administered at two sites over one week, on day 0,3 and 7. If the results of the study show protective titers, it will help in reduction of cost and improving compliance and may help in a big way towards reducing the disease burden. The study will also help manufacturers of ARVs by providing guidance in taking steps to adopt the abridged regimens recommended in the current WHO expert consultation on rabies [10,11].

Human Biologicals Institute (HBI), a division of Indian Immunologicals Limited, Hyderabad, is one of the manufacturers of modern cell cultured ARV for use in humans. Abhayrab®, a purified vero cell cultured rabies vaccine (PVRV) manufactured by HBI, is an inactivated ARV that contributes in a big way towards meeting the requirement of the vaccine in India as well as many other countries in Asia and other continents. This helps in ensuring PEP coverage to a great extent. Since the launch of Abhayrab in the year 2000 from its manufacturing facility at Udhagamandalam (Ooty), Tamil Nadu, the company has been striving hard to cater to the requirement for ARV. In the last 15 years HBI has ramped up its capacity successfully. The supply of Abhayrab® increased from >16 million doses in the period 2004-2009 to >32 million doses in the period 2009-2014. The supply was further increased to >52 million doses in the period 2014-2019. HBI has also commenced supply from its new and modern facility at Karkapatla, Telangana and is making all efforts to meet the requirement of the country and the rest of the

world.

While providing PEP in time is essential in preventing rabies in humans exposed to suspect rabid animals, other means are equally important to reduce the transmission and incidence of the disease. The elimination of human rabies mediated by dogs is attainable through multipronged approach with use of existing safe and effective human and veterinary vaccines and application of different preventive modalities with a sound understanding of the disease. Globally, all developed countries have achieved this goal whereas Asia and Africa have lagged behind. Mass dog vaccination is considered one of the important modalities for the elimination of canine rabies which will ultimately lead to reduction in transmission of the disease to humans. Current veterinary vaccines used in majority of countries are safe and efficacious and provide economic benefits through large-scale campaigns. Despite longer durations of immunity, turnover of canine populations necessitates that vaccination campaigns are performed regularly to achieve sustainably high proportions of herd immunity. However, the frequency at which such campaigns are being carried out remains unsatisfactory [3,12, and 13].

Mass dog vaccination campaigns, with a target of approximately 70% coverage of the estimated population have been tried successfully at many places. Intensive, widely advertised, large-scale vaccination campaigns yield good results as opposed to protracted, independent, uncoordinated area-by-area approaches. Operative since the 1920s, such canine vaccination programs have been proven effective not only in the developed countries but also in some places in lower income countries. The incidence of reported rabies is now negligible as compared to that in the past in most parts of Americas and Europe after repeated and successful mass animal vaccination efforts. One project in Goa, in India, vaccinates around 100,000 dogs annually. With additional efforts of providing rabies related education to children and responding to reports of dog suspected of carrying rabies, the state has achieved good success in control of rabies in the period 2015 to 2017. Reported cases of human rabies mortality in the state has fallen from 17 in 2014 to two in 2017 [13].

Indian Immunologicals Limited, Hyderabad, is a major supplier of animal anti-rabies vaccine (ARV), brand named ‘Raksharab’. The company had started production of this inactivated BHK cell cultured ARV for use in animals in 1989 at its Hyderabad facility. Currently around 15 million doses of ‘Raksharab’ are supplied per year which caters to a significant part of the requirement of vaccines for vaccination of animals against rabies. The company has been supporting rabies control measures sustainably by regularly arranging free animal vaccination camps and holding awareness campaigns among animal handlers, school going children and other people at high risk.

It is hoped that efforts towards elimination of rabies from India and elsewhere in the world will be enhanced in near future. Indian Immunologicals Limited and its division Human Biologicals Institute continue to cater to the needs for high quality modern cell cultured animal as well as human ARVs from the respective facilities. Continuous efforts are being made to improve the accessibility of the vaccines and improve the vaccination coverage and support all efforts towards eliminating rabies from India as early as possible.

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