Title: ENSURING PROPER AND TIMELY PROPHYLAXIS AGAINST RABIES; HOW FAR CAN WE BRIDGE THE GAPS

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Keywords Animal exposures, rabies, prophylaxis, delay factors

Abstract Rabies is a fatal disease still having high prevalence in India. Though safe and effective biologicals are available for pre-exposure and post exposure prophylaxis, thousands of people die from the disease every year. To achieve the goal to eliminate rabies by 2030, serious efforts have to be made to bridge the gaps in supply, availablity and accessibility of rabies biologicals.

Review Article:

ENSURING PROPER AND TIMELY PROPHYLAXIS AGAINST RABIES; HOW FAR CAN WE BRIDGE THE GAPS?

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ABSTRACT:

Rabies is a fatal disease still having high prevalence in India. Though safe and effective biologicals are available for pre-exposure and post exposure prophylaxis, thousands of people die from the disease every year. To achieve the goal to eliminate rabies by 2030, serious efforts have to be made to bridge the gaps in supply, availability and accessibility of rabies biologicals, find out curative modalities, systematically vaccinate and control the population of dogs to reduce the animal rabies burden below the critical level. Public sector companies like Human Biologicals Institute can play an important role in the effort with help from the government and private players.

Conclusion: Delay in PEP is an important issue and the factors for delay have to be addressed properly in order to prevent rabies and eventually eliminate by 2030.

Key words: animal exposures, rabies, prophylaxis, delay, factors.

Since ancient times 'Rabies' has comfortably settled in India and the concerted efforts to unsettle it have not been successful even after development of effective weapons against it. Though there is no proper record of exact time when rabies had first afflicted India, it is considered very ancient and a causal link between the bite of a rabid animal and a human death from rabies was well recognized almost 4000 years ago.[1]A successful vaccination against rabies was demonstrated by Louis Pasteur in July 1885.[2]It was further improved by many, including David Semple who, while working at CRI, Kasauli, India, developed a Sheep Brain vaccine in 1911 that was then used widely all over the world for vaccination against rabies.[3]Safer anti rabies vaccines could be developed later in 70s and 80s with advent of use of cell culture and successful chronic infection of the cells by rabies virus.[4]Development of a Vero cell (the cell line used for manufacture of successful Polio vaccines) cultured and purified anti rabies vaccine resulted in a safe and dependable weapon against rabies in the form of Purified Vero Cell-Cultured Rabies Vaccine (PVRV) that could be produced at large scale and was also cost effective due to high yield of viral antigen.[5,6,7]

With continuous efforts to improve therapeutics against rabies, initially Anti-Rabies Serum (ARS)[8,9,10]and then Rabies Immunoglobulins (RIGs) were found to be effective in cases where Anti-Rabies vaccine (ARV) alone was not able to prevent development of rabies.[11,12]It was also found that, proper local treatment of the bite wound is also essential in getting better results, i.e. reducing rabies incidence.[13,14]Modern highly purified equine origin Rabies Immunoglobulins (ERIGs) could circumvent the high cost of Human origin Rabies Immunnglobulins (HRIGs) as they were found to be both safe and effective.[15,16]Later, efforts have been made to develop effective monoclonal antibody (mAb) preparation against rabies surface glycoprotein[17,18,19]. But it is yet to make its way to clinical practice in a big way. Only one such product, a monovalent mAb developed by an Indian manufacturer has been licensed for use with added precaution for monitoring of its efficacy and safety during post marketing use[20]. As a cocktail of polyvalent mAb is considered an ideal mAb for field use against rabies[21], more data is being awaited and further improvement may be needed for mAbs currently in use or under clinical development. Whether these products can bring down the costs as expected can only be ascertained after more information becomes available. Some antivirals (e.g. Favipiravir, code named T-705) have been tried successfully against rabies virus in mice model, but yet to be tried in humans[22]. Though SiRNAs have been tried against rabies by in vitro and in vivo models and show some prospects, there has not been any good progress yet to prove clinical efficacy.[23]Surprisingly, there have not been enough effort towards evaluating safety and efficacy of intrathecal HRIG, post animal exposure, as a modality of prophylaxis or treatment, which theoretically seems a good approach to neutralize rabies virus in CNS, the principal site of its pathogenicity. No treatment protocol except palliative methods are currently recommended by WHO as there has not been

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any consistent positive result despite the claim about the success of the Milwaukee protocol.[26]Thus, despite a lot of progress, a successful cure for rabies still eludes us. Where as prophylactic arsenals are available against rabies, good therapeutic measures for its treatment and cure are yet to be developed. The war against rabies is heavily dependent on preventive measures, including pre-exposure and post-exposure prophylaxis and reducing and preventing the transmission of rabies among animals and from them to humans. Over all, though India has been successful to a great extent in controlling rabies, it is yet to make significant progress towards elimination of the disease, as some hurdles still remain un-cleared.

A major step towards rabies elimination can be taken by addressing the burden and transmission of the disease in animals.[27] It has long been targeted and still remains a key component under One Health approach towards eliminating Rabies by 2030.[28]However, practical hurdles prevent achievement of much success in this field. But it is a point to be noted that the countries that are successful in eliminating rabies, mostly in western hemisphere, have been able to do it and much has to be learnt from them.[16,28] Though India has its own problems, the country cannot achieve the target of eliminating rabies, without success in animal birth control and animal vaccination.[27,28]

The recent government efforts for a 'Swachh Bharat' may help in reducing the menace of increasing stray dog population by curtailing the amount of food waste being thrown here and there. It is anticipated that a clean India will strive for reduction of prevalence of animals on the streets. In India, dogs are responsible for most cases of human rabies. However, the measures to control dog population and vaccinate them have been taken up only in some areas, mostly restricted to urban pockets.[29]Efforts towards implementing these cumbersome and practically difficult procedures have not been taken up in large scale yet. Vaccinating the large population (to cover more than 70% of the dogs of the area consistently, as laid down by WHO) of dogs in India does not look feasible in the short term.[29,27,28] However, this is a practical and more meaningful measure to move forward towards elimination of rabies.[28]Overall, this has been found to be economical and cost worthy towards reducing the rabies burden both in animals and humans.[28,30]Indian manufacturers, including Indian Immunologicals Limited, can contribute by increasing production to meet the requirement. As these manufacturers have been supplying the inactivated rabies vaccines for animals at a low price, they can be helpful in bridging this gap without exorbitant economic burden on the country.

Disease control programs are difficult to implement without availability of reliable data, especially about the burden of the disease and the population at risk. Due to lack of proper continuous surveillance, proper current estimation about incidence or prevalence of rabies in India is not available. The last systematic estimate was available from a WHO sponsored survey carried out in 2003, and published in 2007. The burden in India was found to be at around 20,000 deaths per year, the highest in a country, in the world.[31]A similar survey started in 2017 is expected to provide the current data once the results are published. Going by an expert guestimate, death from rabies in India, currently, could be around 5000 per year.[16]It appears like some significant reduction but the target of elimination of rabies from India by 2030 still looks like a distant dream. If found to be true, it should be considered a significant achievement none the less, made possible by united efforts on all fronts. But, principally, it can be attributed to increased timely intervention, including the use of rabies biologicals. Though more and more animal bite victims today are able to have a timely access to ARV and RIG (mostly ERIG), still a significant proportion of them are not that fortunate.[32,33]More efforts are required to increase the coverage of availability of anti-rabies biologicals and making them available as early as possible. Human Biologicals Institute, a division of Indian Immunologicals Limited, has been striving to contribute to this cause and keep on improving every successive year. The company keeps making efforts to make the rabies biologicals more accessible and affordable. However, there is a limit to how far the cost of ARVs and RIGs can be reduced. This is due to the costs involved in raw materials, production, logistics and overheads.

With current availability of ARVs at district level hospitals in most of the states, the scenario is much better than it was two decades back. But this has to be taken further by making ARVs and RIGs available at block and gram panchayat level. Even if an animal bite victim of category II or III takes only one dose of ARV as soon as possible after the exposure, it may help in the cause if further treatment can be made available later, as soon as possible, at a district level government hospital or other center. It is pragmatic to encourage administration of the first ARV dose, at the earliest, at the nearest possible place after exposure (where RIG is not required or unavailable) to a suspect rabid animal. The person should take an intramuscular dose of ARV available at the nearest hospital or medical store after consulting a doctor if intradermal vaccination is not feasible.[28]The cost may be reimbursed through some

mechanism if the person has to purchase it, but this early intervention is likely to help in more than one way in preventing development of rabies. The early visit to a facility dispensing ARV may improve the likelihood of proper wound care than the person would have got, which might have got delayed if he would have waited till visiting the nearest government / private set up dispensing Intradermal ARV and RIG. As per the information available from publications on post exposure experience in India and elsewhere, it can be presumed that early wound care and administration of first dose ARV will result in significant reduction in incidence, provided further post exposure care (including administration of RIG when required) is completed at a proper place and time, as most cases of animal exposure get no or delayed treatment at present.[30,31,32]

Another strong advocacy that can be made towards reducing rabies incidence is to make provision for pre exposure prophylaxis. Initially it can be provided to those who are willing and are able to afford it. Intradermal regimens can make pre-exposure prophylaxis quite affordable if group of persons come forward for it together and it is properly planned. A single vial with 1 ml diluent can be used for five people for two 0.1 ml doses and thus 10 people (of any age group) can complete pre-exposure prophylaxis (0.1 ml intradermal at 2 sites at days '0', '7,' '21' or '28')[7] with 6 (0.2 ml x 3 x 10 = 6.0 ml) vials. With requirement of only 2 more 0.1 ml intradermal doses per person, in case of post-exposure, or re-exposure, this actually can result in significant cost reduction. For the estimated 17.4 million people who fall victim to animal exposure every year in India,[8] requiring post exposure prophylaxis, even if a fraction of them have to be covered by pre-exposure vaccination, the reduction can work out to a very significant sum in terms of government or private expenditure.

In this regard, it is also time to consider childhood pre-exposure prophylaxis in the form of anti-rabies vaccination by evaluating a regimen that can make it logistically achievable by co-administration with other childhood vaccines.[33,34] From the available publications on use of ARV in humans,[35,36] a pre exposure prophylaxis regimen with administration of I.D. or I.M. doses on day '0', '28' and '56' (at 6 weeks, 10 weeks, 14 weeks of age) may also be safe and effective in generating good immediate protection and long term immunological memory that will produce good anamnestic response on administration of two post exposure/ re-exposure ID or IM doses on day 0 and 3 as per current practice. As some experts are now advocating that two pre-exposure doses on day '0' and '21' may be enough,[6] based on some reliable data, it is anticipated that only two doses at day '0' and '28' may also be given along with other vaccines (either at 6 weeks and 10 weeks or at 10 weeks and 14 weeks of age). These schedules may become the practice in future after proper studies are conducted to prove their safety and efficacy.

For post exposure prophylaxis, the suggested 'one week four site ID regimen'[37] or shorter duration IM regimens (to be completed in one or two weeks with less number of visits) may also become common practice one day. These will also reduce the cost significantly and help in achieving significant reduction in rabies incidence by ensuring better compliance.

When it comes to providing preventive care, the existing awareness about rabies and its prevention among the mass as well as the doctors and other healthcare providers is still far from desirable. To take comprehensive knowledge on prevention of rabies to each healthcare professional (HCP) in India, considerable efforts have to be made through medical curriculum, publications and other educative material as well as general media which can reach the busy medical fraternity and other HCPs. Public awareness has to be improved through media as well as two way communicative sessions. In this aspect, targeting children and youth, especially through schools/ colleges may be a better approach as it is likely to bring in better practice and implementation.[38]

Coming to involvement of our healthcare systems in One Health approach for elimination of rabies, it looks like a missed opportunity that rabies is not a notifiable disease under Integrated Disease Surveillance Programmme (IDSP) in India.[39] Inclusion of rabies in IDSP and making it a notifiable disease may help in making the doctors more aware and feel responsible towards prevention of rabies in addition to gathering more reliable information regarding the disease. On the other hand, increase in public awareness about disease will not only help in getting more animal bite victims seek early intervention, it may also make people avoid animal bites that can prevent rabies transmitting bites. Manufacturers of rabies biologicals may get involved and help in this effort towards increasing the public awareness and training and awareness of doctors and other healthcare professionals.

While discussing about the roles played by the manufacturers it may be apt to go to some details that are often overlooked. There is scope for manufacturers to reduce the cost further which has rarely been taken up.

In India, some existing procurement practices prevent manufacturers willing to reduce the cost from doing so because of some additional burden that can be circumvented by cooperation of the procuring authorities and agencies. The manufacture of rabies biologicals entails such procedures that production lead time cannot be reduced beyond a certain point. However, this is overlooked in tender procedures and indents are placed on short notice (often less than 60 days) by many agencies, in government, public as well as private sectors. In addition, hefty penalties are also placed by some for delivery beyond a certain time line which is not practicable looking at the fact that at least 6 months are required from start of the procedure to delivery of the vaccine to the customer after obtaining quality certificate from CDL Kasauli. Such practices and the low profit margins (and even losses at times) work as disincentives for manufacturers who thus consider exports a better alternative than selling the products in India. The difficulties and time lags of delivering the vaccines to rural, remote and inaccessible areas add to the challenge of delivering the rabies biologicals at an affordable price. Steps taken in these directions can help improve the situation by reducing the overall cost and making pre-exposure and post-exposure prophylaxis more affordable, available and accessible to the animal exposure victims in India.

It is hoped that, with mutual cooperation and assistance, from all the sectors, the National Rabies Control Program, spearheaded by the government through National Centre for Disease Control (NCDC), can march ahead with success. With support of other authorities and enthusiastic support by APCRI members and other HCPs and partners in 'One Health' approach, significant progress can be made in future towards elimination of Rabies from India by 2030.

Declaration of Conflict of Interest: The authors declare that they work for a subsidiary of National Dairy Development Board, manufacturing rabies biologicals for both human and animal use (at separate facilities)

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