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Review Article

Large-Scale Pre-Exposure Prophylaxis for Children for Rabies Elimination: Is it the Right Approach?

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A B S T R A C T

A global framework for eliminating dog-mediated human rabies by 2030 has been developed by the World Health Organization (WHO) and the World Organisation for Animal Health (WOAH), in collaboration with other partners. Most Asian countries where rabies is endemic have controlled human rabies by focusing on human rabies prophylaxis; therefore, human rabies incidence can be brought down, but not rabies elimination. There has been an attempt to focus on PrEP in children, as children account for a significant proportion of exposures to dogs and deaths due to rabies. In this communication, we discuss the pros and cons of relying on PrEP in children to eliminate rabies, where dog-mediated rabies prevails. Large-scale PrEP for children is not simple and easy to implement, and technical challenges should not be ignored. PrEP of the child population should not distract from controlling and subsequently eliminating rabies at source, i.e., dog rabies.

Keywords: Rabies, Vaccine, Children, Control, Elimination, Prevention, Prophylaxis

Introduction

Rabies is present on every continent except Antarctica. It is estimated that rabies causes 59,000 human deaths annually across the world.[1] The burden of rabies is higher in Asian and African countries, with 40–50% of rabies deaths occurring in children under 15 years.[1,2]Multiple sectors have to be involved in the prevention and control of rabies. This should include the provision of post-exposure prophylaxis (PEP) to exposed patients, control of rabies in the reservoir of infection, control of the stray dog population, pre-exposure prophylaxis (PrEP) of people at high risk of exposure, and public awareness and education. Although it is widely accepted that dog vaccination is the most cost-effective way to prevent human rabies, given that dogs are the primary reservoir and source of human rabies, most rabies-endemic countries have been controlling human rabies by focusing on human rabies prophylaxis.

Since the development of the human diploid cell culture vaccine in the late 1960s, concentrated and purified cell culture and embryonated egg-based vaccines (CCEEVs) have proved to be very effective in preventing rabies, which can be used for both PEP and PrEP.[3] Modern rabies vaccines (CCEEVs) were initially administered only intramuscularly (IM). However, the high cost of CCEEVs and the large number of patients who required PEP in rabies-endemic countries were impediments to its widespread use. To reduce the cost of CCEEVs without compromising vaccine efficacy, intra-dermal (ID) regimens, which use a fraction of

the IM dose, were introduced in rabies-endemic countries with resource constraints. Over the past three decades, results from several clinical trials have confirmed the safety, immunogenicity, and efficacy of the ID route.[4,5,7,8] People taking chloroquine for malaria treatment or prophylaxis may have a reduced response to IDRV, and these patients should receive the vaccine intramuscularly.[4] The direct cost of the vaccine is reduced by 60–80% compared with standard intramuscular rabies vaccination.[5,6,7] The intradermal route of administration is preferred in low- and middle-income countries (LMICs) for both PEP and PrEP, given its cost-effectiveness compared to the intramuscular route. An anamnestic response to booster doses of vaccine is seen in persons who have taken PEP or PrEP.[8,9] In the event of exposure to a rabies-infected animal, PrEP subsequently helps in a rapid immune response after administering 2 doses of vaccine. It avoids the need for passive immunity, which is important in LMICs, where the availability and affordability of rabies immunoglobulin are limited.

Pre-exposure prophylaxis (PrEP) helps prime the immune system and the development of memory cells. PrEP is recommended by the WHO, especially for high-risk groups such as residents or travelers to rabies-endemic areas with limited access to timely and adequate PEP or individuals employed in high-risk occupations.[2] In 2018, WHO shortened the recommended PrEP schedule from three to two visits per week (1-site intramuscular injection on days 0 and 7, or 2-site intradermal injection on days 0 and 7).[2] Short 1-week schedules were as effective as longer schedules that can take between 3 and 12 weeks to complete.10 It has several advantages compared to the previous PrEP regimen, viz., easy to remember, user-friendly, cost-effective, short duration, and high compliance rate. Based on available data, an anamnestic response after the 2-dose series occurs 3 years after the primary series of 2 visits.[10,11] However, an anamnestic response over 3 years after the shortened 2-visit series has not been evaluated.[12] Some European countries have made rabies vaccination mandatory for those assigned to diplomatic or technical missions to rabies-endemic countries with limited access to timely and adequate PEP, and sometimes they may have to leave on short notice. There is an attempt to explore the feasibility of single-visit PrEP against rabies. A systematic review suggests that single-visit PrEP schedules confer sufficient protection in most healthy individuals without immunocompromised status when a booster dose of PEP is administered after suspected rabies exposure. Further studies in real-life settings and at-risk populations, including the generation of conclusive data from a randomized controlled clinical trial, are needed to confirm this finding.[13,14]

Although small-scale pilot studies of PrEP in children to reduce the burden of rabies have been conducted in several countries, the feasibility and scope of large-scale PrEP to prevent rabies in children remain unknown. Introducing PrEP at a large scale will be more expensive than other measures such as PEP and mass dog vaccination. PrEP is considered cost-neutral in settings where the incidence rate of dog bites exceeds 5,000 per 100,000 population per year.[15] There is an ongoing discussion to launch a large-scale PrEP scheme for children in some high-burden rabies-endemic countries in Asia to achieve fast-track rabies elimination by 2030, as implementing mass dog vaccination against rabies is either complex, difficult, or slow. A series of technical challenges associated with such short-sighted public health interventions must be discussed before a policy decision is taken for its execution. This communication discusses the pros and cons of depending on PrEP in children for rabies elimination.

Material and Methods

We have done a literature review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist.[16] We searched PubMed and Google using the terms “rabies” AND “pre-exposure” AND “prophylaxis” OR “vaccine”. We have searched for various trials and studies wherein PrEP in children was evaluated. Some of these were modelling trials that compared the cost of PEP and PrEP+ booster doses. We also reviewed WHO position papers and other publications to focus on PrEP. We obtained other references from citations in relevant journals. We found that some studies favour PrEP in children, and some are not in favour of the same due to the cost and compliance factors. Based on the available data, we have attempted to analyse and present arguments both for and against PrEP in children. This is one of the principal objectives of the study. For the present study, 56 published papers and documents were screened and reviewed. Eligibility, exclusion, and inclusion criteria were defined, and we identified 27 relevant, eligible papers to cite as references. The PRISMA statement methodology checklist is depicted in Figure 1.

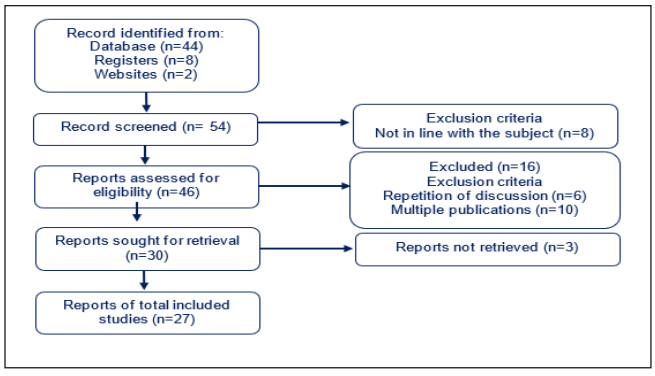

Figure 1.PRISMA statement flow diagram: Summary of systematic search and review process

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Results and Discussions

PrEP plays an important role in preventing rabies in high-risk groups and vulnerable populations, and the decision to use it should be based on the local situation. We found that some studies favor PrEP in children, while others do not, due to cost and compliance factors. There were some pilot studies on the feasibility of PrEP in children in the Amazon region of Peru and the Philippines, which have institutionalized mass dog vaccination, where PrEP in the child population serves as a complementary public health intervention.[9,17] It should be noted that PrEP in Peru was designed to prevent child deaths due to bat rabies in high-risk areas, which demonstrates the value of targeted PrEP.[18,19] More studies are required to assess the cost-effectiveness of PrEP in regions with a high rabies burden, where it can be compared with other interventions. The 2019 modeling study conducted by Hampson et al. concluded that PrEP as part of the extended program of immunization (EPI) is not an efficient use of resources and should only be considered in extreme circumstances, such as in regions where the incidence of rabies exposure is high in populations that cannot access timely PEP.[20] Similarly, Chulasugandha et al. found that the costs of PrEP in children or PEP in exposed individuals were equal when dog-bite incidence was between 2 and 30%, depending on the PEP regimen used.[21] Given the multiple-dose regimens of current vaccines, pre-exposure vaccination is not cost-effective for most countries, warranting the development of a new rabies vaccine.[22] A safe, low-cost, single-dose vaccine that confers lifelong immunity and can be stored at ambient temperatures would be ideal for PrEP.[18,22]

Worldwide, it is estimated that 29 million patients are taking PEP annually due to animal bites or exposure to rabid or suspected rabies animals.[23] This means that in rabies-endemic countries, 290 million people have been vaccinated against rabies over a decade, and memory cells persist in the primed population. The number of patients undergoing PEP is increasing yearly as cost-effective ID schedules have been introduced and it is free of charge in public hospitals. Secondly, the Pediatric Societies and the Advisory Committee on Immunization Practices (ACIP) in rabies-endemic countries recommend that parents consider pre-exposure prophylaxis (PrEP) for their children, as it is affordable these days. The authors of the paper are engaged in continuous medical education programmes on human rabies prophylaxis and advocate that medical practitioners encourage parents regarding PrEP for children, as they may not report back to parents about dog bites due to fear of a painful course of injections, and child rabies cases have been reported in the past. Medical practitioners are encouraged to administer at least two doses of the rabies vaccine to induce memory cells in vaccinees, as per current WHO recommendations.

PrEP poses a series of technical challenges for mass-scale vaccination campaigns. Unlike other vaccine-preventable diseases, in a person who has taken PrEP, booster doses of the rabies vaccine are needed after suspected rabies exposure.[24] This is important in rabies-endemic countries where mass dog vaccination is nonexistent or very low. It will be challenging to determine post-exposure rabies prophylaxis (PEP) in case of exposure to rabid or suspected rabid dogs, as vaccination cards may not be readily available or recall of the date of PEP may be difficult. In rabies-endemic areas, re-exposures are common in childhood and are up to 15% of the exposures.[25] The number of booster doses for revaccination is sometimes determined based on the time elapsed after completion of PrEP or PEP, i.e., ≥ one year.

The Indian Academy of Pediatrics and Lodha et al. have suggested that India can incorporate large-scale pre-exposure rabies vaccination into its national immunization schedule,[26,27] which is easy to say but challenging to implement. Such a premature and short-sighted approach will face problems regarding logistics, public response, integration into the national immunization program, implementation, and follow-up action. Bringing the incidence of human rabies to a minimal level is achievable, but eliminating rabies is not possible with human rabies prophylaxis alone. On the other hand, the family will ignore or neglect vaccinating dogs against rabies, since their children are vaccinated, which may lead to the persistence of the rabies virus in animal reservoirs. This can also lead to a false sense of security in the community. As a result, moving towards rabies-free status will never materialize in a rabies-endemic country like India, and the firefighting business for rabies will remain forever.

For control of rabies, mass dog vaccination campaigns, provision of post-exposure prophylaxis, and education to increase rabies awareness in local communities are essential, apart from PrEP.[18] Controlling rabies at the source is, and will remain, a realistic, cost-effective, and sustainable means of achieving rabies-free status in a community or country. Dog rabies control by mass canine vaccination campaigns combined with intensive surveillance programs has led to a decline in human rabies in many countries.[22] Lodha et al. have recognized that effective control of rabies in dogs is essential for achieving a long-term and sustainable reduction in human rabies cases.[26] Rabies elimination remains a model for operationalizing One Health, as it requires a holistic, multidisciplinary, and multisectoral

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approach. The major problem in dog rabies control in highly endemic countries is that, without a systematic mass dog vaccination campaign with community participation, dog vaccination coverage never exceeds 50% through parenteral vaccination. Free-roaming dogs outnumber pet dogs in many Asian countries due to cultural and religious factors, and catching free-roaming dogs is the most challenging task for parenteral vaccination. The quality of the dog rabies vaccine used in mass vaccination is a critical factor determining the success rate of vaccination campaigns and the durability of the immune status of vaccinated dogs. Robust dog rabies surveillance must be an integral part of a mass dog vaccination program to identify hot spots and evaluate the impact of vaccination campaigns, which is often neglected. To improve vaccination coverage above 70% and break dog-to-dog rabies transmission, introducing oral rabies vaccination of free-roaming dogs in rabies-endemic countries will be a game-changer. However, it should be clear that oral vaccination is supplementary to, not a replacement for, parenteral vaccination.

In summary, the pros and cons of large-scale PrEP among children in rabies endemic countries is presented in Table 1.

Table 1.Pros and Cons of large-scale PrEP among children in rabies endemic countries

PROS	CONS
Targeted PrEP is useful in high-risk areas in endemic countries.	In regions with a high burden of dog-mediated rabies, the cost-effectiveness and logistics challenges of universal PrEP have to be assessed. PrEP consists of multiple dose regimen (three doses/three visits) which may increase non-compliance rate creating false sense of security.
In Rabies endemic countries, PrEP in children can be recommended if the parents can afford Rabies vaccine. This will be useful because children may not always report to parents, if they are exposed to dogs.	Universal PrEP in the government sector, apart from PEP to exposed individuals, will not be feasible because it will be a high financial and logistical burden.
Children who have been administered PrEP have to be given vaccination cards, which have to carefully stored.	Vaccination cards may not be readily available, when the person is exposed to a dog in future creating trouble to medical practitioner to decide PEP schedule in case of re-exposure.
Inclusion of PrEP in EPI is recommended by some Paediatric societies and some doctors in high endemic countries. The discovery of a single-dose, highly potent rabies vaccine for PrEP would be a better option which may happen in future through nanotechnological advancement.	Integration of PrEP in EPI will face logistic problems. Concentrating on PrEP in children may lead to false security and result in neglecting control of disease in the reservoir.
PrEP is recommended for high-risk groups in Amazon region where dog rabies has been eliminated but bat-mediated rabies is emerging and responsible for human rabies.	It has been recommended as a pilot study only. Similarly, pilot studies have been conducted in the Philippines in small scale but not as a substitute of mass dog vaccination.
PrEP is good to prevent human death due to rabies and does not require passive immunisation in case of re-exposure.	Once children are vaccinated against rabies, the family and community will not cooperate in mass dog vaccination maintaining persistence of rabies virus in dog population.

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Limitations

The I/D schedule and PrEP as a voluntary practice or small pilot study are the focus of all published papers. It is rare to discover papers on large-scale PrEP in children as a substitute for mass dog vaccination. It is true that most Asian countries have reduced human rabies mortality by two digits by improving PEP services, public awareness, and dog vaccination programmes. However, there is no proof of concept of achieving rabies-free status focusing on PEP or PrEP without executing a mass dog vaccination campaign with community engagement.

Conclusion

PrEP may serve as a targeted public health intervention for the prevention of rabies in children in hyperendemic areas, which may reduce child mortality due to rabies. It should be emphasized that the number of primed populations against rabies has been increasing because of PEP and PrEP in rabies-endemic countries. Large-scale PrEP for children may require serious thinking regarding logistics and competing priorities of the national immunization program. It may not replace the mass dog vaccination in areas where exposure to dogs carries a risk of rabies transmission. Several technical challenges need to be considered, including PEP in case of re-exposure, unlike other human vaccines included in the national immunization program.

Abbreviations

CCEEV: cell culture and embryonated egg-based vaccines; EPI: Expanded Programme on Immunization; ID: intradermal; IM: intramuscular; PEP: post-exposure prophylaxis; PrEP: Pre-exposure prophylaxis

Authors contribution Conception and design of the study and development of search strategy: GG; manuscript writing, analysis, and interpretation of results: GG, GS, AB, and AG; All authors read and approved the final draft of the manuscript.

Conflict of interest: We declare no competing interests. The positions and opinions presented in this article are those of the authors alone and are not intended to represent the views of their institutions.

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