Cost analysis of implementation of a population level rabies control programme for children in India

Article *in* Clinical Epidemiology and Global Health · February 2023

DOI: 10.1016/j.cegh.2023.101244

7 authors, including:

Abhishek Royal
The Humsafar Trust
17 PUBLICATIONS **99** CITATIONS
SEE PROFILE

Denny John
207 PUBLICATIONS **17,219** CITATIONS
SEE PROFILE

Omesh Kumar Bharti
Indira Gandhi Medical College
169 PUBLICATIONS **340** CITATIONS
SEE PROFILE

Siwi Padmawati
Universitas Gadjah Mada
93 PUBLICATIONS **740** CITATIONS
SEE PROFILE

Clinical Epidemiology and Global Health 20 (2023) 101244

Contents lists available at ScienceDirect

Clinical Epidemiology and Global Health

journal homepage: www.elsevier.com/locate/cegh

Cost analysis of implementation of a population level rabies control programme for children in India

Abhishek Royal [a], Denny John [b,*], Omesh Bharti [c], Diksha Dhupar [d], Diksha [d], Retna Siwi Padmawati [e], Adi Utarini [f]

[a] Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[b] Faculty of Life and Allied Health Sciences, Ramaiah University of Applied Sciences, Bengaluru, India
[c] State Institute of Health and Family Welfare, Department of Health & Family Welfare, Government of Himachal Pradesh, Shimla, India
[d] National Health Systems Resource Centre, New Delhi, India
[e] Department of Health Behaviour, Environment and Social Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[f] Department of Health Policy and Management, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

ARTICLE INFO

Keywords:
Children
Rabies
Implementation cost
Prophylaxis

ABSTRACT

Background: Rabies is an endemic and major public health problem in India. This paper reports cost of implementation of various Pre-Exposure Prophylaxis (PrEP) and Post-Exposure Prophylaxis (PEP) strategies at programmatic level to avert rabies deaths in children in India.
Methods: The cost of implementation of various PrEP + PEP and PEP only regimens recommended by WHO and national guidelines was calculated separately for the first year of implementation for children in the age group of 0–5 years (U-5) and 5–15 years (U-15). The cost was calculated at the level of health facility from government's perspective considering the implementation of the strategies under National Rabies Control Program. All costs were converted into 2020 Indian National Rupee and International Dollars' value using implicit price deflators for Purchasing Power Parities. Base case, scenario and one-way sensitivity analyses were conducted.
Results: The cost of implementation of PrEP regimen is several times higher than all other PEP regimens in children in the age groups of 0–5 years and 5–15 years for the first year of implementation. However, the study also reported use of intradermal route of vaccination and local infiltration of ERIG in wounds only as a cost-saving approach to prevent rabies deaths in children in situations where PEP only strategies are implemented.
Conclusions: There is a need to conduct primary studies in order to obtain data for cost of implementation of shorter regimens in real-time settings.

1. Introduction

Rabies is an endemic and major public health problem in India. It is prevalent across the country except in Andaman & Nicobar and Lakshadweep Islands. Annual human deaths due to rabies are estimated to be around 20,000 and the annual incidence of dog bites to be 1.7% (17.5 million per year) in India.[1] Hence, India contributes approximately one-third of global rabies burden annually. The incidence is high and grossly under-reported in the country due to lack of awareness of preventive measures, poor knowledge of post-exposure prophylaxis, irregular supplies and lack of affordability of ant-rabies vaccines and immunoglobulins and weak surveillance system.[2] Moreover, the prevalence of animal bites is increasing significantly in the country. Thirty-five percent (7000 out of 20,000) of these painful rabies deaths in India occur in children. As children have the propensity to play with stray dogs, they suffer bites on face, hands and other sensitive areas on their bodies.[3] The fatal consequences of the infection can be prevented through adequate wound washing with soap and water along with appropriate administration of optimum quality anti-rabies vaccination and rabies immunoglobulins (RIG) for severe exposures following a bite or exposure.[4]

There are various regimens of rabies vaccines and immunoglobulins currently used in India as post-exposure prophylaxis (PEP) under rabies control programme. Pre-Exposure Prophylaxis (PrEP) and various

* Corresponding author.
E-mail addresses: abhishekroyal2010@gmail.com (A. Royal), djohn1976@gmail.com (D. John), bhartiomesh@yahoo.com (O. Bharti), dollydhupar1@gmail.com (D. Dhupar), diksharathee@gmail.com (Diksha), rspadmawati@ugm.ac.id (R.S. Padmawati), adiutarini@ugm.ac.id (A. Utarini).

https://doi.org/10.1016/j.cegh.2023.101244
Received 30 October 2022; Received in revised form 12 January 2023; Accepted 24 January 2023
Available online 2 February 2023

shorter regimens of PEP are still under naïve phases of implementation in the country.[5] In such a scenario, due to the limited and heterogenous implementation of PrEP and PEP in the country, evidence on costs would be needed for policy makers for increasing coverage, and design cost-effective innovative methods of implementation. A cost analysis of an implementation program can be defined as the cost impact of implementation efforts and is usually calculated at the level of provider or health system perspective.[6] The costs of implementing public health interventions can be calculated across three phases: design, initiation and maintenance. In the design stage, it is calculated at an early stage of implementation for adoption and feasibility of an intervention. Initiation phase during the mid-stage of implementation for penetration which may include training, initiation of supply chains, equipment installation etc, and in the maintenance phase during the late stage to ensure sustainability of the intervention through ongoing technical support, monitoring and evaluation, and troubleshooting.[6,7]

Within the public health context, while there are a growing number of studies detailing the implementation, and its subsequent evaluations, implementation costs are under-represented in the Indian context.[8] We performed an economic evaluation to understand the costs, cost effectiveness and utilization of PrEP + PEP and PEP only strategies to avert rabies deaths in children in India. This paper reports the cost analysis of implementation of PrEP + PEP and PEP only strategies at programmatic level to avert rabies deaths in children in India.

2. Methods

The cost of implementation (COI) of PrEP + PEP and PEP only regimens recommended by WHO and national guidelines (Table 1) was calculated separately for the first year of implementation for children in the age group of 0–5 years (U-5) and 5–15 years (U-15).[4,9] The cost was calculated at the level of health facility from government's perspective considering the implementation of the strategies under the National Rabies Control Program.

The study has been conducted and reported in adherence to the Consensus Health Economic Criteria (CHEC) checklist for partial economic evaluation.[10]

Table 1
Vaccine schedules.

Arms	Strategy	Regimens	Guidelines
Intervention (PrEP I)	PrEP (ID); PEP (ID)	ARV at Day 0, 7 (2-site); ARV at Day 0 (4 site)	WHO Guidelines[4]
Comparator 1 (C1)	PrEP (ID); PEP (ID)	ARV at Day 0, 7, 21 (1-site); ARV at Day 0, 3 (1-site)	National Guidelines[9]
Comparator 2 (C2)	PrEP (IM); PEP (IM)	ARV at Day 0, 7 (1-site); ARV at Day 0, 3 (1-site)	WHO Guidelines[4]
Comparator 3 (C3)	PrEP (IM); PEP (IM)	ARV at Day 0, 7, 21 (1-site); ARV at Day 0, 3 (1-site)	National Guidelines[9]
Comparator 4 (C4)	PEP only (ID)	ARV at Day 0,3,7 (2-site) + RIG in Cat III exposure	WHO Guidelines[4]
Comparator 5 (C5)	PEP only (ID)	ARV at Day 0, 3, 7, 28 (2-site) + RIG in Cat III exposure	National Guidelines[9]
Comparator 6 (C6)	PEP only (IM)	ARV at Day 0, 3, 7, 14–28 (1-site) + RIG in Cat III exposure	WHO Guidelines[4]
Comparator 7 (C7)	PEP only (IM)	ARV at Day 0 (2-site) + Day 7, 21 (1- site) + RIG in Cat III exposure	WHO Guidelines[4]
Comparator 8 (C8)	PEP only (IM)	ARV at Day 0, 3, 7, 14, 28 (1-site) + RIG in Cat III exposure	National Guidelines[9]

ARV = Anti-Rabies Vaccination; ID = Intradermal; IM = Intramuscular; INR = Indian National Rupee; PrEP = Pre-Exposure Prophylaxis; PEP = Post-Exposure Prophylaxis; RIG = Rabies Immunoglobulins.

3. Data inputs

The data inputs were extracted from a published systematic review,[3] independent review of other published and grey literatures, national representative surveys, programmatic reports, and national and state level databases (Table 2). These data inputs and assumptions were also validated by the field experts working in the field of rabies in India.

3.1. Vaccine schedule

The CoI was calculated for nine different regimens in the study: PrEP + PEP (PrEP I, comparator 1, 2 & 3) and PEP only (comparator 4,5,6,7 & 8)[4,9]. PrEP I & comparators 1, 4 and 5 are administered through intradermal (ID) routes while comparators 2,3,6,7 and 8 are administered through intramuscular (IM) routes (Table 1).

3.2. RIG schedule

The RIG is administered in category III exposures in previously unvaccinated individuals at the first visit. The administration of rabies immunoglobulins (RIG) in category III exposures was considered in all the PEP only regimens as no previous exposure to vaccination was assumed. The local plus systemic administration of Equine Rabies Immunoglobulins (ERIG) was considered for the base-case analysis as per the local practices.[11]

3.3. Epidemiological data

Population Size: The children in the age group 0–5 years and 5–15 years were reported to be 113, 645, 000 and 233, 436, 000 respectively as per population projections reported under Census of India, 2011.[12] This estimated population size was used for the calculation.

Annual Bite Incidence**:** A community-based cross-sectional study conducted in the urban parts of Patna reported a dog-bite incidence of 1.62% in under-5 population.[13] The study also reported a dog-bite incidence of 44 in 1000 children in the age group of 5–14 years.[13] As dog is the main animal responsible for most animal bites in the country, this incidence was assumed to be the animal bite incidence in U-5 and U-15 population in India for the base-case analysis. Time horizon of the study was one-year and only one event of animal bite per year was considered for all the bite victims in both the population cohorts.

Distribution of category of exposure**:** A cross-sectional study conducted in anti-rabies vaccines (ARV) clinic in a tertiary care centre in Solapur district reported the profile of animal bite cases in children in 2016.[14] The category I, II and III exposure for children under-5 years of age was reported to be 2.47%, 18.93% and 78.60% respectively. Moreover, the category of exposure was reported to be 0.53%, 26.71% and 72.76% in category I, II and III exposures respectively in the age group of 5–15 years.[14] These estimates are considered for the base-case analyses in both the cohorts.

3.4. Costs and resource utilization

The dose of vaccine utilized during vaccination was considered according to the route of administration and was considered to be the same for both pre-exposure and post-exposure prophylaxes. The average age-specific proportionate weights were calculated from the data reported by Census of India (2011), National Family Health Survey (NFHS-4) 2015–16 and Indian Growth References from 0 to 18-Year-Old children and Adolescents and were used for the calculation of average dose of RIG In the study[12,15,16] (See Appendix 1 and 2).

The procurement cost of one vaccine vial in the state of Madhya Pradesh (MP) by government as reported in the rate contract (2020) on the website of MP Aushadhi and the average procurement cost for a 5 ml vial of ERIG in study states as reported in World Health Organisation-Association for Prevention and Control of Rabies in India (WHO-

Table 2
Data inputs.

Data Inputs	Values		Source
Epidemiology			
Population Age Group	U-5 Cohort	0–5 years	Objective of the study
	U – 15 Cohort	5–15 years	
Population (2021)	U-5	113,645,000	Population Projections for India and States 2011–2036[12]
	U – 15	233,436,000	
Annual bite incidence	U-5	1.62%	N Agarwal 2015[13]
	U-15	4.40%	N Agarwal 2015[13]
Prevalence of Category of Exposure		Cat I = 2.47%	
	U-5	Cat II = 18.93%	Nandimath 2019[14]
		Cat III = 78.60%	
		Cat I = 0.53%	
	U-15	Cat II = 26.71%	Nandimath 2019[14]
		Cat III = 72.76%	
Costs & Resource Utilization			
Amount of eRIG required for children <5 years for local + systemic wound infilteration	1.57 ml		Calculated from NFHS-4 and Khadilkar V[15,16]
Amount of eRIG required for children <5 years for local wound infilteration only	1.5 ml		Bharti 2016[22]
Amount of eRIG required for children 5–15 years for local + systemic wound infilteration	4.33 ml		Calculated from Population Projections for India and States 2011–2036 and Khadilkar V 2019[12,16]
Amount of eRIG required for children 5–15 years for local wound infilteration only	2.64 ml		Calculated from Bharti 2016[22]
Cost per dose of vaccine (1 ml)	INR 250		Rate Contract 2020, MP Aushadhi[17]
Cost per eRIG vial (5 ml)	INR 313		WHO APCRI Survey 2017[18]
Cost per hRIG vial (2 ml, 300 IU)	INR 3700		WHO APCRI Survey 2017[18]
Cost per vial of monoclonal antibodies (2.5 ml)	INR 1970		WHO APCRI Survey 2017[18]
Cost of syringe (per unit)	INR 2.5		Procurement costs (Email communication)
Cost of gloves (per pair)	INR 14		Procurement costs (Email communication)
Cost associated with Human Resources per patient's visit	INR 87.39		Calculated from Data from ARV clinic, Shimla (email communication) National Health System Cost Database of India[19]
Program Management Cost (per capita)	INR 0.2		Calculated from Abbas 2014[20]
Wastage Factor			
Vaccination	30%		Abbas 2014[20]
RIG	15%		Abbas 2014[20]

ARV = Anti-Rabies Vaccination; INR = Indian National Rupee; ID = Intradermal; IM = Intramuscular; PEP = Post-Exposure Prophylaxis; RIG = Rabies Immunoglobulins.

APCRI) survey was used in the study.[17,18]

The procurement costs of syringes (per unit) and gloves (per pair) in 2020 as reported from the state of Himachal Pradesh were used in the current study. The costs of human resources per visit of a bite victim was calculated from the data received from ARV clinic, Shimla and National Health System Cost Database of India (see Appendix 3).[19] The per capita program management costs were calculated from a study on rabies control interventions conducted in the state of Tamil Nadu.[20]

The wastage factor for vaccine and RIG was considered to be 30% and 15% respectively.[17] All costs were converted in to 2020 Indian National Rupee and International Dollars' value using implicit price deflators for Purchasing Power Parities as recommended by Campbell & Cochrane Economic Methods Group (CCEMG).[21]

4. Data analysis

4.1. Base case analysis

The PrEP component in PrEP + PEP strategies was calculated for the total number of the children present in each cohort while PEP component was applied to the calculated number of bite victims only. The costs of vaccine, consumables (including syringes and gloves), human resources and program management were included for the calculation of costs for these strategies.

4.2. Scenario and sensitivity analyses

4.2.1. Scenario analysis

The scenarios evaluated in the study consists of modes of administration of RIG and different pre-approved regimens of RIG for both the cohorts: 1) local infiltration of ERIG in to wounds with no systemic infiltration of the remaining RIG; 2) local and systemic infiltration of Human Rabies Immunoglobulins (HRIG) and; 3) local infiltration of Rabies Monoclonal Antibodies (R-Mab) in category III exposures. The quantity of ERIG for local wound infiltration (scenario 1) in to wound considered from a study in Himachal Pradesh.[22] The average cost of procurement of HRIG was taken as INR 3700 per vial as reported in community survey in WHO-APCRI Survey 2017.[18] The market prices of R-Mab was taken for the calculations.[18] The detailed calculations of ERIG, HRIG and R-Mab is mentioned in Appendices 1 & 2. The variables for scenario analyses are described in Appendices 4. The analyses was conducted in the calculations of cost of implementation of C4, C5, C6, C7 and C8 comparators.

4.2.2. One-way sensitivity analyses

A one-way sensitivity analyses was conducted to test the uncertainty of all the variables on the outcomes. The upper and lower limits of the data inputs extracted from the literature was taken for one-way sensitivity analyses in the study.[10,11,13–15,18–20,23,24] For those variables, there are no additional data inputs in the literature, the upper and lower limits were set at varying degree of variations as per the feasibility of the values viz. ± 10%, ±20% and ±50%. (See Appendix 5).

A tornado diagram was also constructed for every strategy for calculating the cost of implementation for both the cohorts.

5. Results

5.1. Cohort 1: children in the age group of 0–5 years (U-5)

5.1.1. Cost of implementation of PrEP strategies

The total CoI for PrEP (I) was calculated to be USD 2140 million (INR 40, 503 million) at 2020 prices in the U-5 cohort in India. The per capita cost of implementation was calculated to be USD 18.83 (INR 356.4). The total cost of implementation for C1, C2 and C3 strategies was calculated to be USD 2617 million (INR 49,526 million); USD 5322 million (INR 1,00,732 million) and USD 7941 million (INR 1,50,300 million)

respectively (Table 3).

5.1.2. Cost of implementation of PEP strategies

The total cost of implementation for C4, C5, C6, C7 and C8 strategies was calculated to be USD 62 million (INR 1166 million); USD 78 million (INR 1482 million); USD 177 (INR 3349), USD 177 (INR 3349) and USD 218 million (INR 4133 million) respectively (Table 3).

The individual cost of anti-rabies biologicals for U-5 cohort is presented in Appendix 6.

5.1.3. Scenario analyses

The scenario involving the calculation of CoI of local infiltration of ERIG in to wounds only in category III exposures reported in less than 1% reduction in the total CoI in the strategies in comparison to the local plus systemic infiltration of ERIG.

The CoI of scenario 2 involving the use of HRIG in category III exposures was estimated to be 2.3 to 5.5 times higher than the cost of implementation of ERIG as per base-case analysis. Moreover, the cost is 1.3–2 times higher in scenario 3 involving the implementation of R-Mab in comparison with local plus systemic infiltration of ERIG. Therefore, the implementation of ERIG can be considered to be the cost-minimization approach over implementation of HRIG and R-Mab. Moreover, the implementation of local infiltration of ERIG in wound only seems to have not much impact on the total CoI in U-5 cohort. The detailed results are tabulated in Table 4.

5.1.4. Sensitivity analyses

The CoI of PrEP (I), C1, C2 and C3 was sensitive to the following parameters: 1) cost of vaccine vial; 2) costs associated with human resources; 3) vaccine wastage and; 4) cost of gloves. The cost of implementation of PEP strategies (C4, C5, C6, C7 and C8) was sensitive to the following parameters: 1) animal bite incidence; 2) cost of vaccine vial; 3) cost of RIG; 4) vaccine wastage and; 5) RIG utilization. The tornado diagrams are presented in Appendix 8.

5.2. Cohort 2: children in the age group of 5–15 years (U-15)

5.2.1. Cost of implementation of PrEP strategies

The total CoI for PrEP (I) was calculated to be USD 4479 million (INR 84,771 million) in the U-15 cohort in India. The per capita CoI was calculated to be USD 19.19 (INR 363.15). The total CoI for C1, C2 and C3 strategies was calculated to be USD 5474 million (INR 1,03,607 million); USD 11,232 million (INR 2,12,606 million) and USD 16,612 million (INR 3,14,424 million) respectively (Table 3).

5.2.2. Cost of implementation of PEP strategies

The total CoI for C4, C5, C6, C7 and C8 strategies was calculated to be USD 428 (INR 8107), 523 million (INR 9907 million); USD 1085 million (INR 20,532 million); USD 1085 (INR 20,532) and USD 1320 million (INR 24,988 million) respectively (Table 3).

The individual cost of anti-rabies biologicals for U-5 cohort is presented in Appendix 7.

5.2.3. Scenario analyses

The scenario involving the calculation of CoI of local infiltration of ERIG in to wounds only in category III exposures reported in 4–12.5% reduction in the total CoI in the strategies in comparison to the local plus systemic infiltration of ERIG in U-15 cohort.

The CoI of scenario 2 involving the use of HRIG in category III exposures was estimated to be 4 to 10.26 times higher than the CoI of ERIG as per base-case analysis. Moreover, the cost is 1.7–3.2 times higher in scenario 3 involving the implementation of R-Mab in comparison with local plus systemic infiltration of ERIG. Therefore, the implementation of ERIG can be considered to be the cost-minimization approach over implementation of HRIG and R-Mab in U-15 cohort too. However, the implementation of local infiltration of ERIG in wound only is associated with a reduction in the total CoI in U-15 cohort. Therefore, PEP with local infiltration of ERIG in wounds only is a cost-saving approach in category III exposures in previously unvaccinated children in U-15 cohort. The detailed results are tabulated in Table 4.

5.2.4. Sensitivity analyses

The CoI of PrEP (I), C1, C2 and C3 was sensitive to the following parameters: 1) cost of vaccine vial; 2) costs associated with human resources; 3) vaccine wastage and; 4) cost of gloves. The CoI of PEP strategies (C4, C5, C6, C7 and C8) was sensitive to the following parameters: 1) animal bite incidence; 2) RIG utilization; 3) cost of RIG; 4) cost of vaccine vial and; 5) costs associated with human resources. The CoI of intramuscular PEP strategies (C6, C7 and C8) was sensitive to vaccine wastage too. The tornado diagrams are presented in Appendix 8.

Table 3
Results of cost of implementation analysis.

	PrEP (I)	Comparator 1	Comparator 2	Comparator 3	Comparator 4	Comparator 5	Comparator 6	Comparator 7	Comparator 8
Regimen	PrEP + PEP	PrEP + PEP	PrEP + PEP	PrEP + PEP	PEP	PEP	PEP	PEP	PEP
Route of administration	ID	ID	IM	IM	ID	ID	IM	IM	IM
U-5									
Total Cost of Implementation (in millions)	$ 2140 (₹ 40,503)	$ 2617 (₹ 49,526)	$ 5322 (₹ 1,00,732)	$ 7941 (₹ 1,50,300)	$ 62 (₹ 1166)	$ 78 (₹ 1482)	$ 177 (₹ 3349)	$ 177 (₹ 3349)	$ 218 (₹ 4133)
Per Capita cost of Implementation	$ 18.83 (₹ 356.40)	$ 23.02 (₹ 435.80)	$ 46.83 (₹ 886.37)	$ 69.87 (₹ 1322.54)	$ 0.54 (₹ 10.26)	$ 0.69 (₹ 13.04)	$ 1.56 (₹ 29.47)	$ 1.56 (₹ 29.47)	$ 1.92 (₹ 36.36)
Cost of implementation per victim	$ 1162.30 (₹ 22,000.03)	$ 1421.24 (₹ 26,901.23)	$ 2890.66 (₹ 54,714.37)	$ 4313.10 (₹ 81,638.45)	$ 33.45 (₹ 633.15)	$ 42.53 (₹ 804.96)	$ 96.12 (₹ 1819.28)	$ 96.12 (₹ 1819.28)	$ 118.59 (₹ 2244.67)
U-15									
Total Cost of Implementation (in millions)	$ 4479 (₹ 84,771)	$ 5474 (₹ 1,03,607)	$ 11,232 (₹ 2,12,606)	$ 16,612 (₹ 3,14,424)	$ 428 (₹ 8107)	$ 523 (₹ 9907)	$ 1085 (₹ 20,532)	$ 1085 (₹ 20,532)	$ 1320 (₹ 24,988)
Per Capita cost of Implementation	$ 19.19 (₹ 363.15)	$ 23.45 (₹ 443.84)	$ 48.12 (₹ 910.77)	$ 71.16 (₹ 1346.94)	$ 1.83 (₹ 34.73)	$ 2.24 (₹ 42.44)	$ 4.65 (₹ 87.96)	$ 4.65 (₹ 87.96)	$ 5.66 (₹ 107.05)
Cost of implementation per bite victim	$ 436.04 (₹ 8253.30)	$ 532.92 (₹ 10,087.18)	$ 1093.58 (₹ 20,699.31)	$ 1617.30 (₹ 30,612.26)	$ 41.70 (₹ 789.26)	$ 50.96 (₹ 964.50)	$ 105.61 (₹ 1998.98)	$ 105.61 (₹ 1998.98)	$ 128.53 (₹ 2432.84)

HR = Human Resource; PrEP (I) = PrEP (Intervention); $ = US Dollars; ₹ = Indian National Rupee.

Table 4
Results of scenario analysis in cost of implementation analysis.

	Comparator 4	Comparator 5	Comparator 6	Comparator 7	Comparator 8
Regimen	PEP	PEP	PEP	PEP	PEP
Route of administration	ID	ID	IM	IM	IM
Scenario 1 (Local wound infilteration of ERIG)					
U-5 Cohort					
Total Cost of Implementation (in millions)	$ 61 (₹ 1157)	$ 78 (₹ 1474)	$ 177 (₹ 3341)	$ 177 (₹ 3341)	$ 218 (₹ 4124)
Per Capita cost of Implementation	$ 0.54 (₹ 10.18)	$ 0.69 (₹ 12.97)	$ 1.55 (₹ 29.40)	$ 1.55 (₹ 29.40)	$ 1.92 (₹ 36.29)
Cost of implementation per victim	$ 33.21 (₹ 628.67)	$ 42.29 (₹ 800.49)	$ 95.88 (₹ 1814.80)	$ 95.88 (₹ 1814.80)	$ 118.35 (₹ 2240.20)
U-15					
Total Cost of Implementation (in millions)	$ 374 (₹ 7080)	$ 469 (₹ 8880)	$ 1031 (₹ 19,505)	$ 1031 (₹ 19,505)	$ 1266 (₹ 23,962)
Per Capita cost of Implementation	$ 1.60 (₹ 30.33)	$ 2.01 (₹ 38.04)	$ 4.41 (₹ 83.56)	$ 4.41 (₹ 83.56)	$ 5.42 (₹ 102.65)
Cost of implementation per bite victim	$ 36.42 (₹ 689.32)	$ 45.68 (₹ 864.56)	$ 100.33 (₹ 1899.05)	$ 100.33 (₹ 1899.05)	$ 123.25 (₹ 2332.91)
Scenario 2 (Use of HRIG)					
U-5 Cohort					
Total Cost of Implementation (in millions)	$ 340 (₹ 6438)	$ 357 (₹ 6754)	$ 455 (₹ 8621)	$ 455 (₹ 8621)	$ 497 (₹ 9405)
Per Capita cost of Implementation	$ 2.99 (₹ 56.65)	$ 3.14 (₹ 59.43)	$ 4.01 (₹ 75.86)	$ 4.01 (₹ 75.86)	$ 4.37 (₹ 82.75)
Cost of implementation per victim	$ 184.74 (₹ 3496.74)	$ 193.82 (₹ 3668.56)	$ 247.40 (₹ 4682.87)	$ 247.40 (₹ 4682.87)	$ 269.88 (₹ 5108.27)
U-15 Cohort					
Total Cost of Implementation (in millions)	$ 4396 (₹ 83,198)	$ 4491 (₹ 84,998)	$ 5052 (₹ 95,623)	$ 5052 (₹ 95,623)	$ 5287 (₹ 1,00,080)
Per Capita cost of Implementation	$ 18.83 (₹ 356.41)	$ 19.24 (₹ 364.12)	$ 21.64 (₹ 409.63)	$ 21.64 (₹ 409.63)	$ 22.65 (₹ 428.72)
Cost of implementation per bite victim	$ 427.95 (₹ 8100.15)	$ 437.20 (₹ 8275.38)	$ 491.86 (₹ 9309.87)	$ 491.86 (₹ 9309.87)	$ 514.78 (₹ 9743.73)
Scenario 3 (Use of R-Mab)					
U-5 Cohort					
Total Cost of Implementation (in millions)	$ 128 (₹ 2432)	$ 145 (₹ 2748)	$ 244 (₹ 4616)	$ 244 (₹ 4616)	$ 285 (₹ 5399)
Per Capita cost of Implementation	$ 1.13 (₹ 21.40)	$ 1.28 (₹ 24.18)	$ 2.15 (₹ 40.61)	$ 2.15 (₹ 40.61)	$ 2.51 (₹ 47.51)
Cost of implementation per victim	$ 69.78 (₹ 1320.88)	$ 78.86 (₹ 1492.70)	$ 132.45 (₹ 2507.01)	$ 132.45 (₹ 2507.01)	$ 154.92 (₹ 2932.41)
U-15 Cohort					
Total Cost of Implementation (in millions)	$ 1380 (₹ 26,120)	$ 1475 (₹ 27,920)	$ 2036 (₹ 38,545)	$ 2036 (₹ 38,545)	$ 2272 (₹ 43,001)
Per Capita cost of Implementation	$ 5.91 (₹ 111.89)	$ 6.32 (₹ 119.60)	$ 8.72 (₹ 165.12)	$ 8.72 (₹ 165.12)	$ 9.73 (₹ 184.21)
Cost of implementation per bite victim	$ 134.35 (₹ 2543.00)	$ 143.61 (₹ 2718.24)	$ 198.26 (₹ 3752.73)	$ 198.26 (₹ 3752.73)	$ 221.18 (₹ 4186.58)

ARV = Anti-Rabies Vaccination; ID = Intradermal; IM = Intramuscular; INR = Indian National Rupee; PEP = Post-Exposure Prophylaxis; RIG = Rabies Immunoglobulins.

6. Discussion

Our analysis shows that PrEP (I) strategy was reported to be very cost-effective from quasi-societal and quasi-health systems' perspectives over all IM and ID PEP only strategies in children in the age groups 0–5 years and 5–15 years in India,[25] it has higher CoI than PEP only strategies. The CoI of PrEP (I) strategy was reported to be lower than all other IM and ID PrEP strategies in both the age groups.

The administration of ERIG in category III exposures in PEP only strategies was reported to be the cost-saving approach over administration of HRIG and R-Mab. The huge costs associated with HRIG and its lesser availability could be responsible for its unaffordability and therefore, limits its access to the bite victims as per the data inputs used in our analysis. This unrealistic high costs of HRIG has been reported to be beyond the affordability of even higher income groups.[18] As newer formulations of ERIG have almost equal efficacy and safety as HRIG, implementation of ERIG can be a cost-saving approach in settings where PrEP strategies cannot be implemented. Moreover, the local infiltration of ERIG in to wounds only in category III exposures in previously unvaccinated children has been reported to be cost-neutral over local plus systemic infiltration of ERIG in both the cohorts. Though the strategy involving local infiltration of ERIG in wound has not been reported to reduce the CoI in U-5 cohort, this has been reported to reduce CoI by 4–12.5% in PEP only strategies in children in the age group of 5–15 years. A study conducted in Shimla concluded that local infiltration of RIG in wound only can be considered in times of non-availability in the market or unaffordability by poor patients.[22,26] Therefore, local infiltration of ERIG in wounds only could be a resource and cost-saving strategy in resource constrained settings[27] and in the context of India.

National PrEP programs have been implemented in Peru and Philippines. The program in these countries has been shown to prevent rabies deaths in children due to bats in high-risk areas in Peru. The program has also proven that PrEP interventions are effective in preventing rabies deaths in settings where rabies control in animal reservoirs is challenging.[28] The implementation of canine vaccination intervention is challenging in India as a result of uncontrolled dog population and reservations against culling of dogs. Costs associated with canine vaccination has been estimated to be 3 to 10 times higher the ARV in humans in a study in India.[20] A modelling study reported that canine vaccination interventions have to be maintained at a coverage rate of 70% over two decades to be effective in India.[29] Moreover, this strategy has to be boosted by dog population control measures to reduce the number of dog bites as well as cost of PEP in bite victims.[30] Therefore, it is difficult to control rabies in animal reservoirs in the current situation. These evidence also supports the implementation of PrEP strategies in children in India.

6.1. Limitations

The data inputs were extracted from local and regional community-based studies and used in the analysis of our cohorts. However, the data inputs were extracted from representative studies similar to Indian context, and were also validated by the field experts working in the field of rabies in India. The study also did not consider the regional variations and challenges in implementation of the strategies. The costs related to system-wide and environmental interventions including supply chain management systems were not included in the calculation of costs. The costs were also not calculated for subsequent years. The cost of implementation would have been significantly lower in the consequent years due to vaccination requirements for the birth cohort only. The study also did not consider any variations in health budgets, logistics and resource procurement for rabies control in the respective states.

Future research can focus on identifying and developing costs on; supply-chain management for multiple years, and health budgets across several states to provide state-specific COI estimates.

7. Conclusion

The cost of implementation of PrEP regimen is several times higher than all other PEP regimens in children in the age groups of 0–5 years and 5–15 years for the first year of implementation. Our study also reported use of intradermal route of vaccination and local infiltration of ERIG in wounds only as a cost-saving approach to prevent rabies deaths in children in situations where PEP only strategies are implemented. There is a need to conduct primary studies in the future for calculating the cost of implementation of shorter regimens in real-time settings.

Funding

Abhishek Royal was funded under the WHO-TDR Special Program on Implementation Research of Tropical Diseases for his MPH at Faculty of Medicine, Public Health and Nursing, Univesitas Gadjah Made, Yogyakarta, Indonesia. This work was part of the fulfilment of his MPH program.

Ethics approval

The study was approved by Medical and Health Research Ethics Committee (MHREC), Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada – Dr. Sardjito General Hospital (Ref. No. KE/FK/1240/EC/2020) and locally by Sigma Institutional Review Board, India (IRB Number: 10034/IRB/20–21).

Declaration of competing interest

Dr Omesh Bharti is a rabies expert and currently affiliated as State Epidemiologist in State Institute of Health and Family Welfare, Department of Health & Family Welfare, Government of Himachal Pradesh, Shimla, India. He has contributed towards conceptualization of the study, providing expert opinion, development and validation of decision tree model and reviewing the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cegh.2023.101244.

References

1 Sudarshan M, et al. Assessing the burden of human rabies in India: results of a national multi-center epidemiological survey. *Int J Infect Dis*. 2007;11:29–35. https://doi.org/10.1016/j.ijid.2005.10.007.
2 Kole AK, Roy R, Kole DC. *'Human Rabies in India: A Problem Needing More Attention', Bulletin of the World Health Organization*. World Health Organization; 2014:230. https://doi.org/10.2471/BLT.14.136044.
3 John D, Royal A, Bharti O. Burden of illness of dog-mediated rabies in India: a systematic review. *Clin. Epidemiol. Glob. Health*; 2021 [Internet]. 2021 Jun 1 [cited 2021 Jun 24];12:100804. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213398421001123.
4 World Health Organization (WHO). Rabies vaccines and immunoglobulins: WHO position April 2018. Available at: http://apps.who.int/iris/bitstream/10665/259533/1/WER9248.pdf?ua=1; 2018. Accessed July 5, 2020.
5 Shewale A, Nale T, Daptardar M, Tiwari S. A case for pre-exposure prophylaxis of high-risk groups against rabies in India. *J Commun Disord*. 2021;53(1):110–116.
6 Sohn H, Tucker A, Ferguson O, et al. Costing the implementation of public health interventions in resource-limited settings: a conceptual framework. *Implement Sci*. 2020;15:86.
7 Proctor E, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. *Adm Pol Ment Health*. 2011;38(2):65–76. https://doi.org/10.1007/s10488-010-0319-7. Springer.
8 Roberts SL, Healey A, Sevdalis N. Use of health economic evaluation in the implementation and improvement science fields—a systematic literature review. *Implement Sci*. 2019;14(1):72.
9 NCDC National Rabies Control Programme. National rabies control programme. Available at: https://ncdc.gov.in/index1.php?lang=1&level=1&sublinkid=146&lid=150.
10 CHEC list: Consensus health economic criteria – research – maastricht university [internet] [cited 2020 Dec 10]. Available from: https://www.maastrichtuniversity.nl/research/caphri/our-research/creating-value-based-health-care/chec-list-consensus-health-economic.
11 Sudarshan MK, Ashwath Narayana DH. Background paper for developing a policy for the use of rabies biologicals and vaccination of humans in India. *Indian J. Publ. Health NLM (Medline)*. 2019;63:S51–S53. https://doi.org/10.4103/ijph.IJPH_378_19.
12 SRS based abridged life tables. Census of India, 2014-18, Available at: https://censusindia.gov.in/Vital_Statistics/SRS_Life_Table/SRS%20based%20Abridged%20Life%20Tables%202014-18.pdf; 2011.
13 Agarwal N. Epidemiology of dog bites in Patna: cross sectional study. *Indian J. Community Fam. Med.* 2015;1. Issue 02. 2015. Available at: https://www.ijcfm.org/temp/IndianJCommunityFamMed1270-6095449_165554.pdf.
14 Nandimath VA. Anti-rabies prophylaxis among children attending ARV clinic in a tertiary care center, Solapur, India, 2019 *Int J Med Sci Publ Health*. 2019;8(9):742–745. Available at: http://www.ijmsph.com/fulltext/67-1560953960.pdf.
15 International Institute for Population Sciences (IIPS) and ICF. National family health survey (NFHS-4), 2015-16: India. Mumbai: IIPS. Available at: http://rchiips.org/nfhs/NFHS-4Reports/India.pdf; 2017.
16 Khadilkar V. Indian Growth References from 0-18-year-old children and Adolescents - a comparison of two methods, 2019 *Indian J. Endocrinol. Metabol.* 2019;23(6):635–644. https://doi.org/10.4103/ijem.IJEM_555_19.
17 Rate Contract Report. Madhya Pradesh Aushadhi, directorate of health services, government of Madhya Pradesh, India [Accessed on 18th April 2021]. Available at: http://mpaushadhi.mp.gov.in/HISUtilities/dashboard/dashBoardACTION.cnt?groupId=MTU=&dashboardFor=RFdI&hospitalCode=998&seatId=10001&isGlobal=1&isPreview=0.
18 Sudarshan MK, Madhusudana SN, Mahendra BJ, et al. Indian multicentric rabies survey 2017. Bangalore. Available at: http://www.apcri.org/pdf/WHO-APCRI Rabies Survey, 2017 - Final Report.pdf; 2018.
19 Average number and monthly salaries of different human resource categories at various levels of the health system across different states in India. In: *National Health System Cost Database of India*. PGIMER, School of Public Health; 2018. Available at: https://www.healtheconomics.pgisph.in/costing_web/index.php?action=price.
20 Abbas SS, Kakkar M, Rogawski ET. Costs analysis of a population level rabies control programme in Tamil Nadu, India, 2014 *PLoS Neglected Trop Dis*. 2014;8(2).
21 CCEMG. EPPI-centre cost converter v.1.4 [internet] [cited 2020 Sep 29]. Available from: https://eppi.ioe.ac.uk/costconversion/.
22 Bharti OK, Madhusudana SN, Gaunta PL, Belludi AY. Local infiltration of rabies immunoglobulins without systemic intramuscular administration: an alternative cost effective approach for passive immunization against rabies. *Hum Vaccines Immunother*. 2016;12(3):837–842. https://doi.org/10.1080/21645515.2015.1085142. Available from:.
23 Vernekar SP. A study of dog bites among children in the rural area of Goa, India. *J Prev Med Holist Health*. 2018;4(1):20–23. https://doi.org/10.18231/2454-6712.2018.0006, 2018.
24 Agarwal N, Reddajah VP. Epidemiology of dog bites: a community-based study in India. *Trop Doct*. 2004;34(2):76–78, 2004.
25 Royal A, John D, Bharti O, et al. A cost-effectiveness analysis of pre-exposure prophylaxis to avert rabies deaths in school-aged children in India. *Vaccines*. 2023;11:88. https://doi.org/10.3390/vaccines11010088.
26 Bharti OK, Madhusudana SN, Wilde H. Injecting rabies immunoglobulin (RIG) into wounds only: a significant saving of lives and costly RIG. *Hum Vaccines Immunother*. 2017;13(4):762–765. https://doi.org/10.1080/21645515.2016.1255834. Taylor and Francis Inc.
27 Hampson K, Abela-Ridder B, Bharti O, et al. Modelling to inform prophylaxis regimens to prevent human rabies. *Vaccine*. 2019;37(Suppl. S1):A166–A173.
28 Streicker DG, Recuenco S, Valderrama W, et al. Ecological and anthropogenic drivers of rabies exposure in vampire bats: implications for transmission and control. *Proc Biol Sci*. 2012 Sep 7;279(1742):3384–3392. https://doi.org/10.1098/rspb.2012.0538.
29 Totton SC, Wandeler AI, Zinsstag J, et al. Stray dog population demographics in Jodhpur, India following a population control/rabies vaccination program. *Prev Vet Med*. 2010 October 1;97(1):51–57. https://doi.org/10.1016/j.prevetmed.2010.07.009.
30 Abbas SS, Kakkar M. Rabies control in India: a need to close the gap between research and policy. *Bull World Health Organ*. 2015;93(2):131–132. https://doi.org/10.2471/BLT.14.140723.