

Research Article

Safety Assessment of World's First Novel Cocktail of Two Monoclonal Antibodies in WHO Category III Animal Bite Patients at Maulana Azad Medical College, New Delhi, India

Agarwal A¹; Agarwal A²; Mohan A¹; Dutta T^{3*}; Mahajan M³; Desai S³; Kumar D¹

¹Department of Paediatrics, Maulana Azad Medical College, New Delhi, India

²Hindu Rao Hospital, Delhi, India

³Department of Vaccines, Zydus Lifesciences Ltd, Ahmedabad, India

*Corresponding author: Trayambak Dutta

Department of Vaccines, Medical Advisor, Zydus Lifesciences Ltd, Ahmedabad, India.

Tel: 8939719805

Email: Trayambak.Dutta@ZydusLife.com

Received: March 06, 2024

Accepted: April 23, 2024

Published: April 30, 2024

Introduction

Rabies, a viral disease transmitted through animal bites, lurks as a silent threat in over 150 countries. This near-fatal infection infiltrates the central nervous system, causing excruciating symptoms and ultimately death if left untreated [1]. Though preventable through vaccination, rabies claims thousands of lives annually, primarily children in Asia and Africa [2]. The ma-

Abstract

Background: Rabies, a zoonotic disease, poses a significant global public health challenge, and Post-Exposure Prophylaxis (PEP) is crucial for prevention. Monoclonal Antibodies (mAbs) have emerged as a promising alternative to Rabies Immunoglobulins (RIGs) due to their high efficacy and standardized manufacturing process.

Materials & Methods: A prospective, open-label post-marketing surveillance study was conducted at, Maulana Azad Medical College (MAMC), New Delhi on patients with WHO category III suspected rabid animal bites. TwinRab™, a novel cocktail of docaravimab and miromavimab, was administered at a dosage of 40 IU/kg in and around the wound, along with the Anti-Rabies Vaccine (ARV). Adverse Events (AEs) were graded using FDA Toxicity grading.

Results: In this study, 200 subjects received TwinRab™ with a 100% completion rate. Three (1.5%) patients showed solicited local AEs, and two (1%) patients showed solicited systemic AEs, which were resolved after appropriate treatment intervention. The overall tolerability assessment showed positive ratings from doctors (94%) and patients (74%).

Conclusion: The post-marketing surveillance study demonstrated the safety of TwinRab™ in patients who experienced Category III suspected rabid animal bites, thereby supporting its potential as an alternative option for the post-exposure prophylaxis in the management of animal bite for the prevention of rabies.

Keywords: Rabies; Post-exposure prophylaxis; TwinRab™; Safety assessment; Adverse events.

Abbreviations: AEs: Adverse Events; ARV: Antiretroviral; CRFs: Case Report Forms; DALYs: Disability-Adjusted Life Years; EAPC: European Association of Political Consultants; EDC: Electronic Data Capture; ERIG: Equine Rabies Immunoglobulin; FDA: Food and Drug Administration; HRIG: Human Rabies Immunoglobulin; ID: Infectious Diseases; mAbs: Monoclonal Antibodies; PEP: Post-Exposure Prophylaxis; RIGs: Rabies Immunoglobulins; SAEs: Serious Adverse Events; TEAEs: Treatment-Emergent Adverse Events; WHO: World Health Organization

majority of human rabies transmissions, approximately 99%, are due to exposure to infected dogs, resulting in fatal outcomes [1]. According to the National Center for Disease Control, in 2019, global rabies-related Disability-Adjusted Life Years (DALYs) were 782,052.30, which was 45.4% in 1990, and their Estimated Annual Percentage Change (EAPC) was -0.55% [3]. Rabies is a

significant public health issue, causing around 59,000 deaths each year worldwide [4]. Dogs cause most of human infections, emphasizing the importance of widespread dog immunization initiatives [1]. Individuals under the age of 15 are the most affected by this catastrophe, making up 40% of the victims [3]. India is a significant global hotspot, accounting for 36% of worldwide deaths, with an estimated 18,000-20,000 fatalities annually [4]. Underreporting and misdiagnosis exacerbate the situation, indicating that the actual burden could be greater [5]. The economic cost amounts to US\$8.6 billion yearly, but the human cost is incalculable [6]. The data highlights the critical necessity for enhanced initiatives in dog vaccination, public awareness campaigns, and better access to post-exposure prophylaxis to achieve a rabies-free future [7].

The World Health Organization (WHO) recommends post-exposure prophylaxis (PEP) for category II exposure involves vaccination only, and for rabies endemic countries, even this turns out to be a significant cost [8]. Recently, this cost has been minimized by using the updated Thai Red Cross Intradermal Regimen instead of the Essen intramuscular Regimen, which is predominantly used in Asia and recently also in India [9]. The World Health Organization (WHO) categorizes animal bites based on their severity and potential for rabies transmission: Category I (No exposure): Touching or feeding animals, licks on intact skin. Category II (Minor exposure): Nibbling of uncovered skin, minor scratches or abrasions without bleeding. Category III (Severe exposure): Single or multiple transdermal bites or scratches, licks on broken skin, mucous membrane contact with saliva [10]. The WHO recommendation for PEP of category III exposures consists of both rabies vaccine and rabies immunoglobulins (RIGs). RIGs are limited to only those individuals who have not been previously treated with vaccine [11].

There are two types of serum-derived RIGs (human [HRIG] and equine [ERIG]) that have been available for decades, and recently, one humanized Monoclonal Antibody (mAb) based RIG has been licensed in India [12]. WHO points out that around 25% exposures need to be given RIGs in endemic countries, but less than 1% end up receiving it [13].

In India and Thailand, only 2–3% of category III animal bite victims receive RIGs as part of PEP [14]. This is because these RIGs are available at high cost only and are always in limited supply; having been derived from serum, they are associated with the risk of blood-borne pathogens; furthermore, horse-derived RIGs have also been associated with anaphylactic reactions and serum sickness, which lately have been minimized by the use of Fragment Crystallizable (Fc)-deleted ERIG preparations [14]. In India, ERIG is used more frequently because it is less expensive than HRIG. These serious limitations have led WHO to recommend the development of alternative therapies [15].

Despite the availability of vaccines and immunoglobulins for rabies prevention, these treatments are often inaccessible to those in need, particularly in regions with limited access to medical care [16]. Furthermore, the current vaccines have limitations, including barriers to adherence to recommendations, confusion about risk categories, and noncompliance with recommendations for repeated titre checks [17].

A novel approach called TwinRab™ has been developed to address the challenges of rabies prevention. TwinRab™ is a combination of two monoclonal antibodies, docaravimab and miromavimab, which are mouse monoclonal antibodies targeting specific epitopes within antigenic sites II and III of the rabies

virus glycoproteins [18]. Extensive preclinical and clinical studies have demonstrated the safety and non-inferiority of TwinRab™ to HRIG (Human Rabies Immunoglobulin) in terms of protective effect [18]. It has been approved for use in India and is considered a significant advancement in the field of rabies prevention, offering a promising alternative to existing treatments [18].

A Phase 3, Randomized, Open-label, Noninferiority Trial evaluated the safety and efficacy of the TwinRab™ (cocktail of monoclonal antibodies Docaravimab & Miromavimab) in patients with WHO category III exposure from suspected rabid animals [19]. The study confirmed that TwinRab™ is non-inferior to HRIG in terms of providing an unbroken window of protection up to day 84 [19]. The responder rates for TwinRab™ and HRIG were 90.21% and 94.37% in the per-protocol population, respectively [19]. The Geometric Mean of RFFIT titres on day 14 were 4.38 and 4.85 IU/mL for TwinRab™ and HRIG, respectively [19].

The present study was conducted to assess the safety of the TwinRab™ (cocktail of monoclonal antibodies Docaravimab & Miromavimab) in category III animal bite patients. The initial findings emphasize the vital significance of examining safety parameters in real-world scenarios and significantly improving our understanding of the intervention's safety profile beyond the controlled conditions of Phase III trials.

Materials and Methods

Study Design

In this open-label post-marketing surveillance study, the safety of the cocktail of monoclonal antibody Docaravimab & Miromavimab (TwinRab™) in combination with Anti-Rabies Vaccine (ARV) was assessed in patients who received treatment for Category III animal bite at Maulana Azad Medical College, New Delhi. The study was approved by the institutional ethics committee and was conducted in accordance with the Declaration of Helsinki and its subsequent revisions, Good Clinical Practice (GCP) guidelines, and other applicable local regulatory guidelines.

Objective

The objective of this study was to assess the safety of TwinRab™, a combination of mAb Docaravimab and Miromavimab, in patients according to WHO guidelines for Category III suspected rabid animal bites at the end of the 35th day and Day 0 immunization.

Study Participants

A total of 200 healthy subjects (aged > 2 years) who were not previously administered anti-rabies vaccine or had no history of animal bites in the past were enrolled for the assessment of safety of the study vaccine (TwinRab™). Eligible subjects were males and females who fell under WHO Category III exposure(s) by a suspected rabid animal < 72 hours prior to enrollment and < 24 hours if exposed to the face, neck, hand, or fingers, and treatment with the study vaccine was initiated as per the discretion of the principal investigator. Exclusion criteria for the participants included a history of any clinically significant disease (pulmonary, endocrine, autoimmune, psychiatric, cardiovascular, hepatic, or kidney) which may interfere with the study outcomes, a history of thrombocytopenia or known bleeding disorders, subjects with known major congenital defects or serious chronic illness, subjects with a history of thrombocytopenia or known bleeding disorders, and subjects who had participated in

any other clinical study within the last 30 days. All subjects gave written informed consent before randomization. If the subject was a minor (aged 2-17 years), an assent form along with a Legally Authorized Representative (LAR) form had to be obtained by the subject's parents or guardians. The subjects were free to withdraw from the study at any time without compromising their relationship with their study doctor. During the screening procedure, subject's demographics and medical & vaccination history were checked including vital signs (blood pressure and respiratory rate) and physical examination. The eligible subjects were allocated to receive a cocktail of monoclonal anti-rabies antibody (Docaravimab & Miromavimab) on day 0 along with ARVs. ARV injections were administered by the Intradermal (ID) route, following the updated Thai Red Cross Schedule (on days 0,3,7, and 28). The vaccination was performed by trained medical site study personnel. Each subject received a single dose of 40 IU/kg body weight of TwinRab™ from the available 2.5 ml vial. TwinRab™ was infiltrated around the bite wound or wounds along with the ARV on Day 0. Routine general and systemic examination was also performed on day 0, 3, 7, and 28.

Ethical Committee Approval

The study was registered in the CTRI on 02/11/2022 with registration number CTRI/2022/11/046994 and obtained approval from the independent ethics committee of Maulana Azad Medical College and Associated Hospital, New Delhi (Ref. No.: F.1/EC/MAMC/94/06/2022/06 Dated 09th Jan 2023).

Procedure

In this study, 200 individuals with suspected rabies exposures falling under WHO category III were given a single dosage of 40 IU/kg body weight of TwinRab™ from a 2.5 ml vial. On the first visit, the ARV and TwinRab™ were infused around the bite wound or wounds. All unsolicited and solicited adverse events were thoroughly collected, recorded, and reported for the entire 35-day trial period. The severity of AEs associated with rabies treatment was assessed using the FDA Toxicity Grading Scale, and all AEs associated with the rabies vaccine were defined using the vocabulary of MedDRA Version 26.0.

Data Capturing and Statistical Analysis

An Electronic Data Capturing (EDC) system was utilized to transition patients' data from physical Case Report Forms (CRFs) to electronic CRFs. This enabled efficient and accurate data collection, storage, and management. Subsequently, statistical analysis was conducted using SAS®, Version 9.4 (SAS Institute Inc., USA). The collected data were processed and analyzed using appropriate statistical methods. Statistical analyses involved the generation of associated tables, listings, and figures to summarize and present the study's findings.

Safety Assessment

The safety of the studied vaccines was assessed by recording the Adverse Events (AEs) occurring during the study. All abnormalities found in clinical examination were noted as AEs. The solicited (injection site & systemic) AEs were recorded for 7 days post-vaccination & unsolicited (other) AEs were recorded for 35 days (+7 days) following the final dose of the PEP regimen for rabies.

Results

Overall, 200 subjects were enrolled in the study and received a single dose of 40 IU/kg body weight of World's first Cocktail

of RmABs TwinRab™. All 200 subjects (100%) completed the study, with no exclusions or losses to follow-up among the patients (Table 1).

Demographic and Baseline Characteristics

Overall, the mean age was 29.5 (\pm 12.77) years (males: 78% (n=156); females: 22% (n=44)). All subjects were physically examined by investigator and found normal at the time of enrollment. The majority of subjects were in adolescents (aged \geq 13 and \leq 17 years; 81%) followed by child (aged \leq 12 years; 18.5%), geriatric population (aged $>$ 65 years; 8.5%) and adults (\geq 18 and \leq 65 years; 0.5%). The details of baseline characteristics and history of bite wound were summarized in Table 2 and Table 3.

Table 1: Disposition of participants.

	Statistics	TwinRab™
Number of subjects enrolled	N	200
Number of subjects in safety population	N	200
Number of subjects who completed the study	n (%)	200

Abbreviations: N = Number of subjects in the safety population which is used as the denominator to calculate percentages; n = Number of subjects for specific category.

Table 2: Demographic and baseline characteristics.

Characteristic (Unit)	Statistics	TwinRab™ (N = 309)
GENDER		
Male	n (%)	156 (78.00)
Female	n (%)	44 (22.00)
Age (Years)		
	N	200
	Mean (SD)	29.5 (12.77)
	Median	28.0
	IQR (Q1, Q3)	(20.0, 38.5)
	Min, Max	6.0, 67.0
Height (Cm)		
	N	200
	Mean (SD)	164.1 (11.52)
	Median	168.0
	IQR (Q1, Q3)	(160.0, 172.0)
	Min, Max	125.0, 185.0
Weight (Kg)		
	N	200
	Mean (SD)	57.3 (15.61)
	Median	57.0
	IQR (Q1, Q3)	(50.0, 66.0)
	Min, Max	19.0, 125.0
Age Group		
Child (\geq 5 and \leq 12 years)	n (%)	17(8.50)
Adolescent (\geq 13 and \leq 17 years)	n (%)	20(10.00)
Adult (\geq 18 and \leq 65 years)	n (%)	162(81.00)
Geriatric (>65 years)	n (%)	1(.50)
Vital Signs		
Respiratory Rate: Beats/Min		
	N	200
	Mean (SD)	17.3 (1.29)
	Median	17.0
	IQR (Q1, Q3)	(16.0, 18.0)
	Min, Max	15, 20
Systolic Blood Pressure, MMHG		
	N	200
	Mean (SD)	123.1 (8.16)
	Median	124.0
	IQR (Q1, Q3)	(116.0, 129.0)
	Min, Max	102, 143
Diastolic Blood Pressure, MMHG		
	N	200
	Mean (SD)	82.0 (5.94)
	Median	82.0
	IQR (Q1, Q3)	(77.5, 86.0)
	Min, Max	66, 100

Safety

A total of 5 adverse events were reported in 5 (2.50%) subjects with TwinRab™. All reported adverse events have no relationship with the study vaccines. All the reported AEs resolved completely with/without supportive treatment during the study period. Local reactions were observed in 1.5% (n=3) subjects. Reported most local reactions were swelling (1.00%) and erythema (0.50%). These local reactions were mostly reported in adults and geriatrics subjects (aged ≥ 18 and ≤ 65 Years). Two subjects have reported one systemic adverse event "Fever" (1%). There were no Serious Adverse Events (SAEs) or Treatment Emergent Adverse Events (TEAEs) leading to study termination or subject withdrawal from the study. The summary of AEs recorded during the study is described in Table 4.

Overall Tolerability Assessment

The safety population underwent tolerability assessments at the termination of the therapy, with input from both patients

Table 3: History and location of animal bite wound.

History Of Bite Wound	Statistics	Total (N = 309)
Biting Animal		
Dog	n (%)	180 (90.00)
Cat	n (%)	12 (6.00)
Bat	n (%)	0
Monkey	n (%)	8 (4.00)
Mongoose	n (%)	0
No. Of Category Iii Wounds		
Single or multiple transdermal bites	n (%)	200 (100)
Single or multiple transdermal scratches	n (%)	0
Contamination of mucous membrane with saliva	n (%)	0
Location		
Lower body - Legs	n (%)	175 (87.50)
Lower body - Thigh	n (%)	121 (60.50)
Lower body - Buttocks	n (%)	28 (14.00)
Lower body - Feet	n (%)	16 (8.00)
Lower body - Lower back	n (%)	5 (2.50)
Lower body - Genitals	n (%)	3 (1.50)
Lower body - Toes	n (%)	2 (1.00)
Upper body - Fingers	n (%)	9 (4.50)
Upper body - Hands	n (%)	8 (4.00)
Upper body - Upper arm	n (%)	4 (2.00)
Upper body - Head	n (%)	2 (1.00)

Abbreviations: N = Number of subjects in the safety population which is used as the denominator to calculate percentages; N* = Number of subjects in specific age category; n = number of subjects for specific category. Reference Listing 16.2.1

Table 4: Adverse events occurred in the study.

Age Category	Local AEs	TwinRabTM (N = 200)	
		No. of Subjects (%)	No. of Events
Overall	Pain	0	0
	Erythema	1 (0.50)	1
	Swelling	2 (1.00)	2
	Tenderness	0	0
	Induration	0	0

Abbreviations: AE: Adverse Event; N: Number of subjects in the safety population which is used as the denominator to calculate percentages; n: Number of subjects for specific category; N*: Number of subjects in specific age category. **Note:** The percentages are based on the safety population. If a subject had more than one local AEs, they are only counted once for the relevant row of the table for the subject column, but all episodes are included in the episode column. Reference Listing 16.5.1

and doctors. A large majority of patients (74.00%) and doctors (94.50%) rated the therapy's tolerability as "Excellent & Good." Conversely, However, a negligible percentage of patients (0.50%) and doctors (0) rated it as "Fair & Poor." These results underscore the overwhelmingly positive perception of the therapy's tolerability among both patients and doctors, with only a minimal subset reporting a less favorable experience. The present TwinRab™ study exhibited a benign safety profile, with no adverse events attributable to the therapy in any manner in the adult population aged 18 to 65. The therapy was well-accepted, with most patients giving "Excellent & Good" ratings for tolerability.

Discussion

In recent years, the emergence of TwinRab™, a novel Monoclonal Antibody (mAb) cocktail comprising Docaravimab (M777-16-3) and Miromavimab (62-71-3), offers a transformative alternative to conventional Rabies Immune Globulins (RIGs) for Post-Exposure Prophylaxis (PEP). By capitalizing on the inherent advantages of mAbs, TwinRab™ delivers heightened safety, efficiency, and affordability while addressing the global shortage of RIGs [20].

A clinical trial involving 200 participants demonstrated the safety and efficacy of TwinRab™ when administered alongside standard rabies vaccinations. Importantly, there were no severe complications or dropouts observed during the study period, affirming the therapy's suitability for widespread use. The study revealed a disproportionately high male representation among participants, highlighting the importance of promoting gender equity in vaccination initiatives. Dog bites were the primary cause of injuries, particularly affecting the lower limbs, underscoring the need for targeted preventive measures. TwinRab™ was shown to be non-inferior to RIGs in providing continuous protective immunity until Day 84. Although there was a slight increase in adverse events compared to previous trials, the overall safety profile remained commendable. TwinRab™ was administered at a maximum dose of 5000 IUs in this study without any AEs noted. Volume wise 8.33 ml of TwinRab™ was administered in our study as the maximum volume administered so far for TwinRab™ without any AEs noted.

The study by Fan et al. (2022) compared TwinRab™ with RIGs in individuals with suspected rabies exposure, demonstrating comparable levels of protection and safety [21]. Similarly, Kansagra et al.'s (2021) open-label study confirmed TwinRab™'s continuous protection until Day 84, matching the performance of RIGs [19].

Unlike single mAb therapies, TwinRab™ addresses the risk of viral escape by targeting two unique epitopes of the rabies virus glycoprotein. This dual-target approach enhances neutralization capability, even against variants with high mortality rates. Moreover, mAbs display exceptional specificity, minimal cross-reactivity, and favorable pharmacokinetics and pharmacodynamics characteristics, including longer half-lives [22].

The present study assessed the safety of PEP using an anti-rabies product comprising a cocktail of 2 mAbs in combination with a full course of anti-rabies vaccination, in patients with suspected category III rabies exposure. Passive immunization has been an essential component of PEP to prevent rabies for decades. The benefit of RIG in combination with vaccination in PEP of patients with severe bite wounds has been established through scientific evidence. Mollentze et al. (2014) and Ha-

radanhalli et al. (2022) described efforts to prepare rabies immune globulin of human origin. A study by Hobart et al. (2021) led to a dose of 20 IU/kg proven to provide early protection without interfering with the active antibody response to anti-rabies vaccination. TwinRab™ (40 IU/kg) provides good protection against rabies and was found non-inferior to HRIG as per the conducted phase-III study by Zydus Lifesciences, Ahmedabad [23-25].

The study subjects were representative of both sexes and varied age groups. In the present study, the safety profile of TwinRab™ was found to be in line with other published studies, with no serious adverse events reported. The current study reported only fever as a systemic reaction. Similarly, Lang and colleagues, 2014 also showed only fever in a few subjects, whereas other systemic reactions were not observed. The most common local reactions (erythema and swelling) reported were also similar to those reported in other published studies [26]. Based on the present conducted clinical study, the safety and tolerability profile of TwinRab™ is good, with none of the patients reporting pain at the injection site. Haradhanalli et al. 2013 reported that the incidence of local adverse events included pain at the injection site, erythema, itching, and systemic adverse events such as fever, malaise, headache, and body ache [27]. In a comparative safety study of ERIG and HRIG in children at a tertiary care hospital (in India) showed that 42.2% in the ERIG group had adverse events, whereas only 5% in the HRIG group developed adverse events, and the difference was statistically significant [28]. A post marketing surveillance study from IDBG Hospital Kolkata, India with TwinRab™ reported a total of 401 patients with suspected rabid animal bites were recruited wherein 9.9% of the study population had mild, localised, solicited adverse events which resolved completely compared to 2.5% in our study. Neither any systemic adverse events were reported nor was a breakthrough infection with Rabies reported during the entire duration of the study. TwinRab™ was administered at 3800 IU as the maximum dose in this study without any AEs noted compared to a maximum of 5000 IUs administered in this study without any AEs noted. Volume wise 8.33 ml of Twinrab was administered in our study as the maximum volume administered so far for Twinrab without any AEs noted. Further this study reported a mucous membrane exposure with saliva of suspected rabid animal wherein the membrane was directly rinsed with TwinRab™ diluted in normal saline solution with no AEs noted. The overall tolerability of TwinRab™ was excellent or good in more than 90% of subjects as feedback from both investigators & patients in this post marketing study [18].

The current study assessed TwinRab™, a novel combination of monoclonal antibodies, for safety in patients with WHO category III animal bites. Although this Real-World Evidence (RWE) study provided valuable insights, it exhibited a shorter duration compared to prior phases of research. Consequently, the evaluation of long-term events, such as delayed side effects or sustained treatment effects over an extended timeframe, has limited information. To enhance the robustness and comprehensiveness of the findings, it is advisable to implement more extended follow-up periods.

Conclusion

The study evaluated the safety of TwinRab™, a novel cocktail of monoclonal antibodies Docaravimab and Miromavimab, in patients with WHO category III animal bites. The research reported a few solicited adverse events, which resolved completely and were not assessable in terms of causality with TwinRab™

administration. Additionally, no unsolicited or serious adverse events were reported. TwinRab™ demonstrated good tolerability and received positive feedback from doctors. The post-marketing surveillance study suggests that TwinRab™ provides a safe and effective alternative to human and equine derived immunoglobulins, with potential future public health relevance for standardized treatment in Rabies PEP. However, larger clinical trials are needed to further substantiate the safety of monoclonal antibodies in Rabies post-exposure prophylaxis.

Author Statements

Acknowledgements

We express our sincere appreciation and gratitude to Dr. Prachi Sharma and Koshy Jacob, Medical Affairs at Digicare Health Solutions Private Limited (DHSPL), who contributed significantly to the conduct of the Post-Marketing Surveillance (PMS) study.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms.

Financial Support and Sponsorship

This study was supported by Zydus Lifesciences Limited.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Rabies. Who.int.
2. Nyasulu PS, Weyer J, Tschopp R, Mihret A, Aseffa A, Nuvor SV, et al. Rabies mortality and morbidity associated with animal bites in Africa: a case for integrated rabies disease surveillance, prevention and control: a scoping review. *BMJ Open*. 2021; 11: e048551.
3. Gan H, Hou X, Wang Y, Xu G, Huang Z, Zhang T, et al. Global burden of rabies in 204 countries and territories, from 1990 to 2019: results from the Global Burden of Disease Study 2019. *Int J Infect Dis*. 2023; 126: 136–44.
4. Rabies around the world. Cdc.gov. 2020.
5. Rabies. Who.int.
6. Hampson K, Coudeville L, Lembo T, Sambo M, Kieffer A, Attlan M, et al. Estimating the global burden of endemic canine rabies. *PLoS Negl Trop Dis*. 2015; 9: e0003709.
7. The Case for Investment. United Against Rabies.
8. Towards a rabies-free world as unparalleled global initiative gets underway. Who.int.
9. Salahuddin N, Gohar MA, Baig-Ansari N. Reducing cost of rabies post exposure prophylaxis: Experience of a tertiary care hospital in Pakistan. *PLoS Negl Trop Dis*. 2016; 10: e0004448.
10. Scholand SJ, Quiambao BP, Rupprecht CE. Time to revise the WHO categories for severe rabies virus exposures—Category IV? *Viruses*. 2022; 14: 1111.
11. O'Brien KL, Nolan T. The WHO position on rabies immunization – 2018 updates. *Vaccine*. 2019; 37: A85–7.
12. Fan L, Zhang L, Li J, Zhu F. Advances in the progress of monoclonal antibodies for rabies. *Hum Vaccin Immunother*. 2022; 18.
13. Chulasugandha P, Khawplod P, Havanond P, Wilde H. Cost comparison of rabies pre-exposure vaccination with post-exposure

- treatment in Thai children. *Vaccine*. 2006; 24: 1478–82.
14. Bharti OK, Madhusudana SN, Wilde H. Injecting rabies immunoglobulin (RIG) into wounds only: A significant saving of lives and costly RIG. *Hum Vaccin Immunother*. 2017; 13: 762–5.
 15. Kundu B, Meshram G, Bhargava S, Meena O. Cost savings of using updated Thai Red Cross intradermal regimen in a high-throughput anti-rabies clinic in New Delhi, India. *Trop Med Infect Dis*. 2019; 4: 50.
 16. Sreenivasan N, Li A, Shiferaw M, Tran CH, Wallace R, Blanton J, et al. Overview of rabies post-exposure prophylaxis access, procurement and distribution in selected countries in Asia and Africa, 2017–2018. *Vaccine*. 2019; 37: A6–13.
 17. PEP recommendations. *Who.int*.
 18. Manna A, Kundu AK, Sharma Sarkar B, Maji B, Dutta T, Mahajan M. Real-world safety of TwinRab™, the world's first novel cocktail of rabies monoclonal antibodies, in a clinical setting. *Cureus*. 2024; 16.
 19. Kansagra K, Parmar D, Mendiratta SK, Patel J, Joshi S, Sharma N, et al. A phase 3, randomized, open-label, noninferiority trial evaluating anti-rabies monoclonal antibody cocktail (Twin-Rab™) against human rabies immunoglobulin (HRIG). *Clin Infect Dis*. 2021; 73: e2722–8.
 20. Abela-Ridder B. Rabies: 100 per cent fatal, 100 per cent preventable. *Veterinary Record*. 2015; 177: 148–9.
 21. Fan L, Zhang L, Li J, Zhu F. Advances in the progress of monoclonal antibodies for rabies. *Hum Vaccin Immunother*. 2022; 18.
 22. Zorzan M, Castellán M, Gasparotto M, Dias de Melo G, Zecchin B, Leopardi S, et al. Antiviral mechanisms of two broad-spectrum monoclonal antibodies for rabies prophylaxis and therapy. *Front Immunol*. 2023; 14.
 23. Mollentze N, Biek R, Streicker DG. The role of viral evolution in rabies host shifts and emergence. *Curr Opin Virol*. 2014; 8: 68–72.
 24. Haradhanalli RS, Fotedar N, Kumari N, Narayana DHA. Safety and clinical efficacy of human rabies immunoglobulin in post exposure prophylaxis for category III animal exposures. *Hum Vaccin Immunother*. 2022; 18.
 25. Hobart-Porter N, Stein M, Toh N, Amega N, Nguyen H-B, Linakis J. Safety and efficacy of rabies immunoglobulin in pediatric patients with suspected exposure. *Hum Vaccin Immunother*. 2021; 17: 2090–6.
 26. Lang JM, Pawlowski Z, Müller C, et al. First-in-human trial of a novel human monoclonal antibody against rabies virus glycoprotein G. *Antiviral Res*. 2014; 107: 12–18.
 27. Haradhanalli KS, Rao VK, Reddy BV, et al. Safety and immunogenicity of a humanized monoclonal antibody against rabies virus glycoprotein G in healthy adults. *J Med Virol*. 2013; 85: 1–8.
 28. Kansagra K, Parmar D, Mendiratta SK, Patel J, Joshi S, Sharma N, et al. A phase 3, randomized, open-label, noninferiority trial evaluating anti-rabies monoclonal antibody cocktail (Twin-Rab™) against human rabies immunoglobulin (HRIG). *Clin Infect Dis*. 2021; 73: e2722–8.