Active safety surveillance of rabies monoclonal antibody and rabies vaccine in patients with category III potential rabies exposure

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Summary

Background A vero cell-based inactivated Rabies Vaccine (Rabivax-S) and Rabies Human Monoclonal Antibody (Rabishield) have been approved since 2016. A post-marketing surveillance was conducted in India from 2020 to 2021 to gather real world safety data on Rabivax-S and Rabishield.

Methods This was non-interventional active surveillance in patients with category III potential rabies exposure who were administered a post-exposure prophylaxis (PEP) regimen (Rabishield and Rabivax-S) by their healthcare providers (HCPs) as per the dosages and regimens mentioned in the package insert approved by the Indian regulators. The approved schedule for PEP was local infiltration of Rabishield on Day 0 and five doses of Rabivax-S on Day 0, 3, 7, 14, and 28 (Intramuscular route, IM) or four doses of Rabivax-S on Day 0, 3, 7, and 28 (Intradermal route, ID). The primary objective of this surveillance was to generate real-world evidence on the safety and tolerability of Rabishield and Rabivax-S. All patients enrolled in the surveillance were required to report any adverse events (AEs) occurring up to Day 31 after initiation of PEP (administration of Rabishield and the first dose of Rabivax-S) to their HCP.

Findings A total of 1000 patients with category III potential rabies exposure were enrolled across India. 991 patients received the PEP regimen with IM Rabivax-S while 9 received a PEP regimen with the ID regimen. While 32% of the patients were <12 years of age, 11.8% were ≥12 to <18 years of age and 56.2% were ≥18 years of age. The entire PEP regimen was completed by 97.3% of the enrolled patients. A total of 69 AEs were reported in 64 patients. Out of these, 49 AEs in 47 patients were assessed as causally related to the study products (26 with Rabishield and 23 with Rabivax-S). The majority of the AEs were mild and all recovered without any sequelae. One serious adverse event (SAE) of fracture of the hand was reported which was not related to either Rabishield or Rabivax-S. No case of rabies was reported.

Interpretation Rabishield and Rabivax-S have an excellent safety profile and are well tolerated. No participant developed rabies during 31 day follow up.

Funding The PMS was funded by Serum institute of India Private Limited which is the manufacturer of the study products.

Keywords: Rabies vaccine; Rabies human monoclonal antibody; Safety; Post-marketing surveillance

Introduction

Rabies is a 100% fatal yet 100% preventable disease.[1] Pre- and post-exposure prophylaxis with vaccines and immunoglobulins are highly effective in preventing rabies. Rabies disproportionately affects people living in developing countries. Worldwide, there are 59,000 deaths caused by rabies each year, mostly in Asia and Africa,[2,3] 20,000 of them in India alone.[4]

For many years, safe and efficacious rabies vaccines produced in various cell cultures, have been available. In

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Research in context

Evidence before this study

A rabies monoclonal antibody (Rabishield) and vero cell-based rabies vaccine (Rabivax-S) are developed and licensed in India since 2016. Rabishield is the world's first approved rabies monoclonal antibody. The clinical trials conducted for these products are already published and they did not report any safety concerns. We searched PubMed on January 13, 2023, with the terms "Rabies Vaccine", "Rabies Human Monoclonal Antibody", "safety" and "post-marketing surveillance" with no date or language restrictions, and no publications were found.

Added value of this study

To our knowledge, this is the largest PMS study involving 1000 Category III potential rabies exposure patients for Rabies PEP in India in a real-world setting. The PEP regimen containing Rabishield and Rabivax-S (both by IM and ID routes) was found safe and well tolerated by both the adult as well as the pediatric group. Though the exposures were not to confirmed rabid animals, nevertheless, no participant developed rabies during the 31 day follow up.

Implications of all the available evidence

WHO has recommended combined active and passive immunization for post-exposure prophylaxis of category III suspected rabies exposures. Human rabies immune globulin (HRIG) and equine rabies immune globulin (ERIG) are being used for passive immunization for the last several decades however since both are blood-derived products, they have many issues with quality, safety as well as availability. As a result, only 2–3% of category III potential rabies exposures receive any ERIG/HRIG. Failure to give passive immunization can lead to the development of rabies even if the full course of rabies vaccine is administered. Based on the available clinical trial data, WHO stated that Rabishield has more advantages over RIGs like large-scale production with standardized quality, greater effectiveness than RIG, elimination of the use of animals in the production process, and reduction in the risk of adverse events.

This real-world evidence (RWE) study generated additional data on the safety of Rabishield. This RWE data is useful for policy decisions for the use of this product in category III exposure patients especially since the actual use of RIGs is limited, only 2–3% in the developing world.

India, a Vero cell-based rabies vaccine,[5] Rabivax-S was developed which was subsequently authorized in 2016. This vaccine has shown comparable immunogenicity to other cell culture vaccines in pre-exposure,[6] as well as post-exposure schedules[7] by both intramuscular and intradermal routes. It was also prequalified by the World Health Organization (WHO) in 2018.[8]

In the 1960's, the importance of passive immunization in the form of rabies immune globulin (RIG) for post-exposure prophylaxis (PEP) has been established in numerous case reports.[9,10]

The ready-made antibodies in the form of RIGs neutralize the rabies virus in the wounds. The seroresponse (neutralizing antibody titer $\geq$0.5 IU/ml) induced by rabies vaccines reaches 100% by day 14.[7] However, the incubation period of rabies can be as short as 4–6 days, especially in high-risk exposures on the head and neck.[11,12] Therefore, administration of passive immunization in the form of RIGs in the wounds is extremely important to neutralize the rabies virus before vaccine induced immune response is attained. There are several reports where a full regimen of rabies vaccination was given without any passive immunization, the patient developed rabies and subsequently died.[13–17]

For passive immunization two types of RIG are available; human rabies immune globulin (HRIG) and equine rabies immune globulin (ERIG). ERIG is more affordable than HRIG and is used more frequently in developing countries due to cost and availability. However, ERIG causes a higher incidence of adverse events (AEs), including serum sickness and anaphylaxis.[18] Affordability is an important factor in the use of RIG in PEP in developing countries.[19] As per a study in India, only 2.7% of 783 patients with category III bites were prescribed HRIG, and only 10 could afford to receive it.[20] Also, as per other studies, only 2% and 3%, of patients with category III exposures receive any RIG in India and Thailand, respectively.[21,22]

An alternative approach would be to replace polyclonal RIG with a monoclonal antibody capable of neutralizing the virus.

Therefore, a single human monoclonal antibody (mAb) against rabies virus G glycoprotein binding to the most conserved site III was developed in the United States. The safety and efficacy of this fully human IgG1 mAb was first demonstrated in non-clinical studies.[23] Based on this technology, Rabishield was developed in India and its safety was demonstrated in phase 1 clinical study.[24] In the Phase 2/3 clinical study in patients with category III exposures, Rabishield containing PEP regimen was non-inferior to HRIG containing PEP regimen in terms of rabies virus neutralizing antibody activity.[25]

Though in 2002, WHO recommended that cocktails containing at least two mAbs binding to non-overlapping epitopes of rabies virus G glycoprotein should be used for rabies PEP,[26] several studies have shown that Rabishield neutralizes a broad panel of

rabies virus isolates of both canine and bat origin, not only from India but also from other countries across the globe.[23,27] To our knowledge, there is not a single human rabies isolate reported in the world that is known to escape neutralization by Rabishield.

Rabishield was authorized in India in 2016 and was recommended by the Strategic Advisory Group of Experts (SAGE) of WHO in 2018[28] and has been included in the WHO essential medicines list in 2021.[29]

The recent WHO position paper on Rabies vaccines has stated that this mAb neutralizes a broad panel of globally prevalent rabies virus isolates and has encouraged the use of mAb products instead of RIG because of advantages like large-scale production with standardized quality, greater effectiveness than RIG, elimination of the use of animals in the production process, and reduction in the risk of adverse events.[28]

The primary aim of this PMS was to generate real-world safety data for a PEP regimen containing Rabivax-S and Rabishield.

Methods

Active post-marketing surveillance on Rabishield and Rabivax-S in patients with category III potential rabies exposures was conducted at 85 sites across 17 states in India. The objective was to generate additional data on the safety and tolerability of Rabishield and Rabivax-S in patients with category III potential rabies exposure. The study outcomes were incidence of AEs, serious AEs (SAEs), and rabies cases through 3 days after the last dose of the PEP regimen. It was conducted from February 2020 to September 2021.

Ethical aspects

The study was approved by the Indian regulatory authority and Institutional ethics committee of the Translational Health Science and Technology Institute (THSTI), Faridabad, India. The study was conducted in compliance with the principles of the Declaration of Helsinki (2013) and 'Ethical Guidelines for Biomedical Research on Human Subjects' issued by the Indian Council of Medical Research, 2017. Written informed consent was provided by each patient or his/her parents in case of minor participants in addition to assent from children 7 to 17 years of age before enrolment. Since this was a non-interventional study, it was not registered on a clinical trial registry.

Study procedures

This surveillance was conducted at government or private rabies clinics where Rabishield and Rabivax-S were prescribed and administered in routine practice. When a patient with category III exposure from a suspected rabid animal, came to the clinic, he/she was given first aid with proper wound care and tetanus prophylaxis was administered, if necessary. Eligibility was confirmed based on the medical history, clinical examination, eligibility to receive Rabivax-S or Rabishield as per the approved prescribing information, and appropriate understanding of the surveillance.

Rabishield (3.33 IU/kg) was infiltrated in the area around and into all the wounds on Day 0. Rabivax-S was given by IM or ID route as per the site practice. For the IM route, the Essen PEP regimen was followed with five doses of 1 ml on Days 0, 3, 7, 14, and 28 (1-1-1-1-1). For the ID route, the Updated Thai Red Cross Schedule was followed with eight doses of 0.1 ml on Days 0, 3, 7, and 28 (2-2-2-0-2). Rabishield and Rabivax-S were not provided free of cost to the investigators.

The investigators assessed the safety of the participants. Their contact details were with the participants/parents who could report any AE during the study period. At each visit, the physician asked the patients about AEs, and the same were recorded in the electronic case report forms (eCRF). Safety assessments included occurrence of AEs and SAEs through 3 days after the last dose of Rabivax-S PEP regimen. The survival rate on Day 31 was also assessed. The severity, seriousness, and causality assessment of AEs was done by the study investigator based on the available information at the reporting time point.

Study population

The PMS was conducted on 1000 eligible patients with Category III potential rabies exposure who sought medical care at the designated clinics/hospitals. Final eligibility was determined based on the results of the medical history, clinical examination, eligibility to receive Rabivax-S or Rabishield as per the prescribing information, and appropriate understanding of this surveillance study.

Study products

Rabishield (manufactured by Serum Institute of India Pvt Ltd, SIIPL) is a sterile solution of a fully human IgG1 monoclonal antibody directed to rabies G glycoprotein. It is supplied as 2.5 ml vials containing not less than 40 IU/ml (100 IU/2.5 ml vial) and as 1.25 ml vials containing not less than 40 IU/ml (50 IU/1.25 ml vial) of rabies monoclonal antibody. Excipients include citrate buffer (sodium citrate and citric acid) and polysorbate 80, sodium chloride.

Rabivax-S (manufactured by SIIPL) is a sterile, purified inactivated rabies vaccine containing 1 dose of lyophilized powder in a vial and 1 ml of diluent, Sterile Water for Injections in an ampoule. Each dose of 1 ml contains purified rabies antigen (rabies virus Pitman–Moore Strain 3218-VERO adapted and grown on Vero cells, inactivated by using β—propiolactone) not less than 2.5 IU and excipients like sucrose, glycine and human serum albumin (HSA).

A total of 17 commercial batches of Rabishield and 51 batches of Rabivax-S were used in the PMS.

Statistical analysis

With a sample size of 1000, the study provided a 95% probability to detect a product-related AE occurring at a frequency of 0.3%. The safety analysis was conducted on all patients who received at a minimum Rabishield and the first dose of Rabivax-S. Data from Rabivax-S IM route and ID route was also analyzed separately. Descriptive analyses were conducted for safety parameters of AEs and SAEs. The overall proportion of patients reporting at least one AE along with their exact 95% CI and total number of events was tabulated. The missing data was treated as missing and no imputation was done.

Role of funding source

The study was funded by SIIPL. The funder of the study was involved in study design, data interpretation, and writing of the report, but was not involved in data collection and data analysis.

Results

Baseline characteristics and demographics

A total of 1000 patients with category III rabies exposures were enrolled and were part of the safety population and all received Rabishield and the first dose of Rabivax-S on day 0. Out of these, 27 patients did not complete the study treatment regimen of Rabivax-S. A total of 973 patients completed the study regimen, of which 964 (96.4%) patients completed the Rabivax-S IM regimen of 5 doses, while 9 completed the Rabivax-S ID regimen. A total of 4978 doses of Rabivax-S (72 doses ID and 4906 doses IM) and 1594 vials of Rabishield were administered.

The demographic features of patients are shown in Table 1. Among 1000 patients, 661 (66.1%) were male while the mean age was 24.44 years. The age range was 0.2 years–85.1 years. While 32.0% of the patients were <12 years of age, 11.8% were ≥12 to <18 years of age and 56.2% were ≥18 years of age.

	Rabishield + Rabivax-S IM (N = 991)	Rabishield + Rabivax-S ID (N = 9)	Total (N = 1000)
Age (in Years)			
n	991	9	1000
Mean	24.30	38.83	24.43
SD	16.721	20.004	16.798
Min, max	0.2, 85.1	17.7, 81.8	0.2, 85.1
Sex [n (%)]			
Male	658 (66.4)	3 (33.3)	661 (66.1)
Female	333 (33.6)	6 (66.7)	339 (33.9)
Body weight (in kg)			
n	991	9	1000
Mean	47.63	68.89	47.82
SD	20.895	14.173	20.936

Table 1: **Demographic and baseline characteristics—enrolled population.**

Suspected rabies exposures

Most of the patients reported bites with scratches by wild and domestic animals. The majority of patients reported transdermal bites 522 (52.2%) and scratches with bleeding 442 (44.2%). Twenty-four (2.4%) patients reported licking on broken skin whereas exposure of saliva to mucous membranes was reported in 9 (0.9%) patients.

In domestic animal exposures, a total 895 (89.5%) patients had dog bites, and 65 (6.5%) reported cat bites. In wild animals, monkey bites were reported in 34 (3.4%), 2 (0.2%) patients each reported fox and jackal bites, while 1 (0.1%) patient each reported bites by bat and wild pig.

Among these 1000 patients, 586 (58.6%) patients reported a single wound, 276 (27.6%) had two wounds, 86 (8.6%) patients had 3 wounds whereas 52 patients had more than 3 wounds (Table 2).

In 52.1% of patients, the location of the bite/exposure was on a lower limb, whereas 9.8% cases had high-risk exposure involving the head, neck, and face region (Supplementary Table S1). High-risk exposures on head, neck, and face occurred in 15.11%, 13.39% and 5.18% of children below 12 years, ≥12 and <18 years and adults, respectively (data not shown).

Safety results

A total of 69 AEs were reported in 64 patients. Out of these, 49 events were causally related to the study products (26 with Rabishield and 23 with Rabivax-S) (Table 3). Injection site erythema (1.1%) was the most common AE related to Rabivax-S while injection site pain (1.5%) was the most common AE related to Rabishield.

Out of 69 AEs, 68 were of Grade 1 severity while only one was reported as grade 3 (i.e. hand fracture in a pediatric patient). All 49 related AEs were of grade 1 severity (Table 4). All the AEs recovered without any sequelae. There were no AEs related to Rabivax-S administered via the ID regimen.

In terms of age wise distribution, there were 38 AEs in 34 (6.0%) patients in the adult age group (≥18 years), of which 27 events were related to the study products (Supplementary Table S2). Injection site pain was the most common AE related to both Rabishield (1.6%) and Rabivax-S (0.7%). In the <18 years age group, 31 AEs were observed in 30 (6.8%) patients, of which 22 events (5.0%) were related with the study products (Supplementary Table S3). The most common AE related with Rabishield in this group was injection site pain (1.4%) and with Rabivax-S was injection site erythema (2.3%). One (0.2%) SAE of hand fracture was reported in a child which was not related to the study vaccine.

	Total (N = 1000) n (%)
Nature of exposure	
Transdermal bite	522 (52.2)
Lick on broken skin	24 (2.4)
Exposure of saliva to mucous membrane	9 (0.9)
Scratch with bleeding	442 (44.2)
Other[a]	3 (0.3)
Animal type	
Wild	140 (14.0)
Domestic	860 (86.0)
Pet	189 (18.9)
Stray	671 (67.1)
Species	
Dog	895 (89.5)
Cat	65 (6.5)
Monkey	34 (3.4)
Fox	2 (0.2)
Other[b]	4 (0.4)
Number of wounds	
1	586 (58.6)
2	276 (27.6)
3	86 (8.6)
>3	52 (5.2)

[a]Other nature of exposures involved one case each of deep wound, full thickness bite and puncture wound. [b]Other species involved one case each of bat and wild pig and 2 cases of jackal bite.

Table 2: **Summary of rabies exposure.**

Survival rate

In this surveillance, no rabies related mortality was reported in any of the patients across all sites in India. Thus, the survival rate was 100% at 31 days after initiation of PEP.

Discussion

This active surveillance was conducted in 1000 Category III potential rabies exposure patients from 17 states across India. A major strength of this surveillance was a good mix of the adult and pediatric age groups. Approximately 44% of the population enrolled in this surveillance was from the pediatric age group. The PEP regimen containing Rabishield and Rabivax-S was found safe and well tolerated. To the best of our knowledge, this is the largest PMS for PEP of Rabies in India with a diverse population.

Around 44% of the patients were below 18 years of age while 32% of the patients were below 12 years of age. It is known that 40% of people bitten by suspected rabid animals are children under 15 years of age.[30] Around 90% of the cases were caused by dog bites, which is consistent with the earlier studies in India, where the main animals responsible for bites were dogs (96.2%).[31] In our study, 52.1% of the bites were in the lower limb. Sudarshan MK et al. also reported that 56.2% of bites were on the lower limb.[31]

A total of 4978 doses of Rabivax-S and 1594 vials of Rabishield were distributed during this surveillance. Almost all the AEs were mild and all recovered without any sequelae. The most common AEs were local injection site reactions which were consistent with those seen during the pre-licensure studies.[6,7,24,25] Only one SAE was reported in the PMS which was not related with the Rabivax-S and Rabishield. This is in line with clinical studies done on these products. Rabishield was found safe in Phase 1 and Phase 2/3 clinical studies.[24,25] Similarly, Rabivax-S was found safe in Phase 1 and Phase 2/3 studies.[6,7] A recently published study in India in 397 subjects with category III exposure also demonstrated the safety of Rabishield.[32]

The PEP regimen with Rabishield and Rabivax-S was well tolerated by both the adult as well as the pediatric patients. There are no known age differences in the safety profile of rabies biologics. There were no AEs reported in Rabivax-S ID group though only nine patients had received the ID regimen. In general, Rabivax-S was safe both by IM and ID routes.[6,7] The safety of both routes is well established.[33]

Only nine patients had received ID regimen while 991 had received the IM regimen. The ID regimen was introduced in India in year 2006.[34] However, it is mostly used in the government healthcare system while the PMS was conducted in mostly private healthcare facilities where the IM route is majorly used. The rabies vaccine procurement in India in 2017 according to the route of administration was 34% for IM route (mostly private), 34% for ID route (only

	Total (N = 1000)			
	No. of patients (n)	%	(95% CI)	No. of events (E)
Any AE	64	6.4	(4.96, 8.10)	69
Related AEs	47	4.7	(3.47, 6.20)	49
Rabishield	26	2.6	(1.71, 3.79)	26
Rabivax-S	23	2.3	(1.46, 3.43)	23
SAEs	1	0.1	(0.00, 0.56)	1

Table 3: **Overall summary of adverse events.**

System organ class (SOC) preferred term (PT)	Rabishield (N = 1000)				Rabivax-S (N = 1000)			
	n	%	(95% CI)	E	n	%	(95% CI)	E
Patients with at least one related AE	26	2.6	(1.71, 3.79)	26	23	2.3	(1.48, 3.46)	23
General disorders and administration site conditions	26	2.6	(1.71, 3.79)	26	23	2.3	(1.48, 3.46)	23
Injection site erythema	7	0.7	(0.28, 1.44)	7	11	1.1	(0.56, 1.98)	11
Injection site pain	15	1.5	(0.84, 2.46)	15	4	0.4	(0.11, 1.03)	4
Injection site swelling	2	0.2	(0.02, 0.72)	2	5	0.5	(0.16, 1.17)	5
Pyrexia	0				3	0.3	(0.06, 0.88)	3
Discomfort	1	0.1	(0.00, 0.56)	1	0			
Injection site pruritus	1	0.1	(0.00, 0.56)	1	0			

Table 4: **Related adverse events by SOC-PT (Safety population).**

Government), and 32% for both IM and ID (Government/Private).[35]

Though the incubation period of rabies in humans is generally 20–60 days, the fulminant disease can become symptomatic within 5–6 days.[36] Therefore, it is important that no case of rabies was reported in the enrolled population through 31 days. However, based on our data, conclusions cannot be drawn on the efficacy of the products.

One limitation of our study was a short follow up of three days after completion of the PEP. However, the AEs caused by rabies vaccines as well as rabies monoclonal antibody are known to occur within three days of administration and there are no known delayed reactions.[6,7,24,25] Therefore, we believe that the follow up was adequate to detect AEs caused by these products. Another limitation was that rabies exposures were from suspected rabid animals, and not from confirmed rabid animals. In a real-life scenario, it is not possible to trace and test every incriminating animal and therefore, confirmation of rabies in animals is not possible. Since rabies is a 100% fatal disease, PEP is recommended even if such confirmation is not available.

The strengths of our study include a large sample size of 1000 individuals as well as the real-world setting in which it was conducted. All administered products were from marketed lots, so the results obtained can be extrapolated to vaccine and Rabishield batches reaching the general population. To our knowledge, this is one of the largest safety data on rabies PEP in patients of category 3 exposures.

To conclude, the PMS demonstrated that both Rabishield and Rabivax-S have an excellent safety profile and are well tolerated by the patients. No participant developed rabies during 31 day follow up.

Contributors

GK, PSK, DK, BG, CB and AD contributed to the study design and protocol development. AL, AD, JN, CB and BG accessed and verified the data. PSK, JN, CB and AD contributed to the manuscript preparation. The manuscript was finalized with considerable input from all the authors.

Data sharing statement

Individual level participant data will not be made available to others due to privacy concerns.

Declaration of interests

AL, CB, AD, JN, DK, BG and PSK are employees of SIIPL, which manufactures Rabishield and Rabivax-S. CSP is the Chairman and Managing Director of SIIPL. The principal investigator, GK served in an honorary capacity. All other authors declare no competing interests. The study was funded by SIIPL which is the manufacturer of the study vaccine. However, SIIPL did not provide the Rabishield and Rabivax-S free of cost to the investigators. The investigators were paid a fee per participant.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lansea.2023.100207.

References

1 World Health Organization. Rabies: 100 per cent fatal, 100 per cent preventable. Available online at: https://www.who.int/publications/i/item/vr-148; 2015.
2 World Health Organization. *WHO expert consultation on rabies: second report*. WHO technical report series no 982. Geneva, Switzerland: World Health Organization; 2013.
3 Hampson K, Coudeville L, Lembo T, et al, Global Alliance for Rabies Control Partners for Rabies Prevention. Estimating the global burden of endemic canine rabies. *PLoS Negl Trop Dis*. 2015;9:e0003709.
4 Plotkin SA. Vaccine production in human diploid cell strains. *Am J Epidemiol*. 1971;94:303–306.
5 Kulkarni PS, Sahai A, Gunale B, Dhere RM. Development of a new purified vero cell rabies vaccine (Rabivax-S) at the serum institute of India Pvt Ltd. *Expert Rev Vaccines*. 2017;16(4):303–311.
6 Kulkarni PS, Sapru A, D'costa PM, et al. Safety and immunogenicity of a new purified vero cell rabies vaccine (PVRV) administered by intramuscular and intradermal routes in healthy volunteers. *Vaccine*. 2013;31(24):2719–2722.
7 Bose A, Munshi R, Tripathy RM, et al. A randomized non-inferiority clinical study to assess post-exposure prophylaxis by a new purified vero cell rabies vaccine (Rabivax-S) administered by intramuscular and intradermal routes. *Vaccine*. 2016;34(40):4820–4826.
8 World Health Organization. Prequalification of medical products (IVDs, medicines, vaccines and immunization devices, vector

control). Available online at: https://extranet.who.int/pqweb/content/rabies-vaccine-inactivated-freeze-driedrabivax-s.
9 Noury M. On the importance of rabies in Morocco. *Maroc Med.* 1963;42:461–466.
10 Sabeti A, Bahmanyar M, Ghodssi M, Baltazard M. Treatment of rabid wolf bites in Iran. Present situation. *Ann Inst Pasteur (Paris).* 1964;106:303–307.
11 Tinsa F, Borgi A, Jahouat I, Boussetta K. Rabies encephalitis in a child: a failure of rabies post exposure prophylaxis? *BMJ Case Rep.* 2015;2015:bcr2014206191.
12 Ghosh S, Rana MS, Islam MK, et al. Trends and clinico-epidemiological features of human rabies cases in Bangladesh 2006-2018. *Sci Rep.* 2020;10(1):2410.
13 Lin FT, Chen SB, Wang YZ, Sun CZ, Zeng FZ, Wang GF. Use of serum and vaccine in combination for prophylaxis following exposure to rabies. *Rev Infect Dis.* 1988;10(Suppl 4):S766–S770.
14 De Benedictis P, Perboni G, Gentili C, et al. Fatal case of human rabies imported to Italy from India highlights the importance of adequate post-exposure prophylaxis, October 2011. *Euro Surveill.* 2012;17(19):20168.
15 Deshmukh DG, Damle AS, Bajaj JK, Bhakre JB, Patil NS. Fatal rabies despite post-exposure prophylaxis. *Indian J Med Microbiol.* 2011;29(2):178–180.
16 Sangeetha Lakshmi GNS. Rabies: need for active and passive immunisation. *Int J Med Res Health Sci.* 2014;3(1):202–204.
17 Gowda VK, Basavaraja GV, Reddy H, Ramaswamy P. Paralytic rabies following cat scratch and intra-dermal anti-rabies vaccination. *J Pediatr Neurosci.* 2014;9(2):154–155.
18 Wilde H, Chomchey P, Prakongsri S, Puyaratabandhu P, Chutivongse S. Adverse effects of equine rabies immune gobulin. *Vaccine.* 1989;7:10–11.
19 Fang LX, Ping F, Ping du Y, Hui BG, Yan YX. Socioeconomic status is a critical risk factor for human rabies post-exposure prophylaxis. *Vaccine.* 2010;28(42):6847–6851.
20 Gogtay NJ, Nagpal A, Mallad A, et al. Demographics of animal bite victims & management practices in a tertiary care institute in Mumbai, Maharashtra, India. *Indian J Med Res.* 2014;139(3):459–462.
21 Sudarshan MK, Mahendra BJ, Madhusudana SN, et al. An epidemiological study of animal bites in India: results of a WHO sponsored national multi-centric rabies survey. *J Commun Dis.* 2006;38:32–39.
22 Kamoltham T, Singhsa J, Promsaranee U, Sonthon P, Mathean P, Thinyounyong W. Elimination of human rabies in a canine endemic province in Thailand: five-year programme. *Bull World Health Organ.* 2003;81:375–381.
23 Sloan SE, Hanlon C, Weldon W, et al. Identification and characterization of a human monoclonal antibody that potently neutralizes a broad panel of rabies virus isolates. *Vaccine.* 2007;25(15):2800–2810.
24 Gogtay N, Thatte U, Kshirsagar N, et al. Safety and pharmacokinetics of a human monoclonal antibody to rabies virus: a randomized, dose-escalation phase 1 study in adults. *Vaccine.* 2012;30(50):7315–7320.
25 Gogtay NJ, Munshi R, Ashwath Narayana DH, et al. Comparison of a novel human rabies monoclonal antibody to human rabies immunoglobulin for postexposure prophylaxis: a phase 2/3, randomized, single-blind, noninferiority, controlled study. *Clin Infect Dis.* 2018;66(3):387–395.
26 Available online at: https://apps.who.int/rabies/resources/mabs_final_report_WHO_consultation_2002.pdf. Accessed March 11, 2023.
27 Wang Y, Rowley KJ, Booth BJ, et al. Glycoprotein amino acid residues required for human monoclonal antibody RAB1 neutralization are conserved in rabies virus street isolates. *Antiviral Res.* 2011;91(2):187–194.
28 WHO. Rabies vaccines: WHO position paper. *Wkly Epidemiol Rec.* 2018;93:201–220.
29 *World Health Organization model list of essential medicines – 22nd list, 2021.* Geneva: World Health Organization; 2021 (WHO/MHP/HPS/EML/2021.02). Available online at: https://apps.who.int/iris/bitstream/handle/10665/345533/WHO-MHP-HPS-EML-2021.02-eng.pdf. Accessed March 11, 2023.
30 Rabies. https://www.who.int/news-room/fact-sheets/detail/rabies; 2021. Accessed January 4, 2023.
31 Sudarshan MK, Madhusudana SN, Mahendra BJ, et al. Assessing the burden of human rabies in India: results of a national multi-center epidemiological survey. *Int J Infect Dis.* 2007;11(1):29–35.
32 Shivalingaiah A, Shankaraiah R, Hanumanthaiah AN. Safety of new indigenous human rabies monoclonal antibody (RMAb) for post exposure prophylaxis. *Indian J Community Health.* 2018;30(3):196–201.
33 Dreesen DW, Fishbein DB, Kemp DT, Brown J. Two-year comparative trial on the immunogenicity and adverse effects of purified chick embryo cell rabies vaccine for pre-exposure immunization. *Vaccine.* 1989;7(5):397–400.
34 Gongal G, Sampath G. Introduction of intradermal rabies vaccination - a paradigm shift in improving post-exposure prophylaxis in Asia. *Vaccine.* 2019;37(Suppl 1):A94–A98.
35 Sudarshan MK, Ashwath Narayana DH, Jayakrishnappa MB. Market mapping and landscape analysis of human rabies biologicals in India. *Indian J Public Health.* 2019;63(Supplement):S37–S43.
36 Plotkin SA. Rabies. *Clin Infect Dis.* 2000;30(1):4–12.