

Review article

Time interval for booster vaccination following re-exposure to rabies in previously vaccinated subjects

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Background: In rabies endemic areas, re-exposures to rabies are quite common and the incidence could be up to 15%. The recent guidelines of World Health Organization do not specify the duration of protection provided by previous pre- or post exposure prophylaxis. This often puts the treating physician in a dilemma in such cases of re-exposure.

Objective: Study the time interval between primary and booster vaccination in individuals who have taken previously a full course of either pre- or post exposure prophylaxis and are now re-exposed to rabies.

Methods: The data obtained through a literature search using Pubmed and advanced Google search along with data from in house clinical trials were used for analysis. Sixty-six vaccine cohorts spanning more than 27 years from 1983 to 2010 from six countries were studied. The duration of protection offered by previous vaccination was assessed by using a surrogate marker of adequate (≥ 0.5 IU per mL) rabies virus neutralizing antibody levels in the individuals vaccinated either by pre-exposure or post exposure regimens received by intramuscular or intradermal routes.

Results: The proportions of 2,795 subjects who had received prior post-exposure immunization and produced rabies virus neutralizing antibody levels of less than 0.5 IU per mL were 0.07% and 0.14% at the end of the first and third month post primary vaccination. All 577 subjects with previous pre-exposure vaccination had antibody responses above 0.5 IU per mL at the end of the first and third month post primary vaccination.

Conclusion: We concluded that it may be safe for up to three months after previous pre- or post exposure vaccination to not administer boosters to healthy subjects who have been re-exposed to rabies.

Keywords: Booster vaccination, post exposure prophylaxis, pre-exposure vaccination, rabies, re-exposure

In rabies endemic areas, re-exposure to rabies is common with an incidence up to 15% [1]. As rabies is 100% fatal, it is very important to provide timely and correct post exposure prophylaxis (PEP) in such cases. The PEP includes immediate wound cleansing, rabies immunoglobulin injected into and around wounds and rabies vaccination. However, the recent guidelines of World Health Organization (WHO) do not specify the duration of protection provided by previous vaccination i.e. pre-exposure (PrEP) or post exposure prophylaxis (PEP) [2]. Most established Asian animal bite clinics use the arbitrary cut-off of either three or

six months post reliable vaccination when boosters are not deemed to be required [36]. This practice has, however, not been defined in WHO guidelines and creates a dilemma for many attending physicians who are confronted by a potential exposure. This study was conducted to study antibody kinetics in previously vaccinated subjects.

Materials and method

Articles published in peer reviewed national and international journals that could be accessed from Pubmed and Google Scholar were reviewed [3, 5-22]. In-house data of rabies vaccine trials was also perused [4, 23-35]. We focused on the number of patients that had vaccine and who produced an inadequate rabies virus neutralizing antibody (RVNA) concentration < 0.5 IU per mL to a full course of

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vaccination given either intramuscularly (IM) or intradermally (ID), with or without rabies immunoglobulin (RIG) during the first six months. Wherever possible, the RVNA response was studied up to day 365 post vaccination.

Sixty-six vaccine cohorts from six countries (France, Germany, India, Thailand, United Kingdom, and USA) were available. They included 44 cohorts from published studies and 22 cohorts from in house vaccine trials. The span of coverage of the data was about 27 years extending from 1983 to 2010. The vaccines used included human diploid cell vaccine (HDCV), purified chick embryo cell vaccine (PCEC), purified vero cell rabies vaccine (PVRV), and purified duck embryo vaccine (PDEV). These were administered PrEP and PEP and by IM and ID regimens. The vaccines were given with RIGs either equine (21 cohorts) or human (8 cohorts) in PEP regimens. The PEP IM regimen used was the “Gold Standard” intramuscular Essen (1-1-1-1-1) or intradermally the “Thai Red Cross” (TRC) (2-2-2-0-

1-1), “updated TRC” (2-2-2-0-2) and “Oxford” (8-0-4-0-2-1) schedules.

Results

Antibody response to PEP immunisation

Vaccinees who produced a neutralizing antibody concentration of less than the optimal level of 0.5 IU per mL to a full course of vaccination by intramuscularly (IM) or intradermally (ID) with or without rabies immunoglobulin (RIG) were 0.07% and 0.14% at the end of the first and third month post primary vaccination respectively as shown in **Table 1**. All subjects retained detectable titers for up to one year.

Antibody response to PrEP vaccination

Vaccinees with a history of pre-exposure vaccination, all had neutralizing antibody levels above 0.5 IU per mL one and three month later (**Table 2**). All subjects retained detectable titers for up to one year.

Table 1. Antibody response to PEP immunization

Route of administration of vaccine	Enrolment/ Recruitment		RIGs used		Patients with inadequate antibody response					References
	Cohorts	Subjects/ Patients	Cohorts	Subjects/ Patients	Day 28	Day 90	Day 180	Day 365	Total	
Intramuscular	23	1314	12	636	0/1238	0/1051	3/670	9/99	12	3,4,5
Intradermal	32	1481	17	690	2/1268	4/1366	3/719	37/558	46	4,5,6,7,8,9
Total	55	2795	29	1326	2/2506	4/2417	6/1389	46/657	58	-

The numerator is the number of Vaccinees with inadequate antibody response, RVNA concentration < 0.5 IU per mL, and the denominator, number of sera samples tested for RVNA.

Table 2. Antibody response to PrEP vaccination

Route of administration of vaccine	Enrolment/ Recruitment		Patients with inadequate antibody response					References
	Cohorts	Subjects/ Patients	Day 28	Day 90	Day 180	Day 365	Total	
Intramuscular	8	518	0/263	0/33	4 (D135)/37	8+4 (D450)/209	16	10,11
Intradermal	3	59	0/59	0/59	0/33	0/59	-	3
Total	11	577	0/322	0/92	4 (D135)/70	8+4 (D450)/268	16	11

The numerator is the number of Vaccinees with inadequate antibody response, RVNA concentration < 0.5 IU per mL, and the denominator, number of sera samples tested for RVNA.

Discussion

Based on previous studies, we understand that the neutralizing antibody response to PEP and PrEP is usually close to 100% by days 14 and 28. This indeed is a WHO requirement for acceptance of any new tissue culture vaccine. These titers then gradually decline but remain detectable for decades and will rapidly respond to booster injections in virtually all normal hosts. We also assume that an antibody titer above 0.5 IU per mL is important during the first month after a re-exposure. We also believe that, if the antibody level is under the WHO recommended minimum level of 0.5 IU per mL during this initial critical time period, this constitutes a risk factor if no booster response is elicited. It is reassuring to note that virtually all subjects in this large PEP and PrEP groups have antibody levels above 0.5 IU per mL up to the end of the third month.

Conclusion

Thailand and Philippines issued local guidelines that mandate boosters six month after the previous PEP or PrEP in subjects who experienced a new rabies exposure. In Sri Lanka, it is twelve months [1]. Data collected in this study, confirm the practice of using three months cutoff point in normal hosts. The final decision, however, cannot be taken from the attending physician who bears the ultimate responsibility for the patient. A position statement by the next WHO expert committee may well be overdue.

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