

ORIGINAL ARTICLE

**FACTORS AFFECTING COMPLIANCE TO RABIES POST-EXPOSURE
PROPHYLAXIS AMONG PEDIATRIC PATIENTS SEEN AT THE RESEARCH
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KEYWORDS:

Rabies post exposure prophylaxis, rabies immunoglobulin

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Rabies is a viral disease that produces uniformly fatal encephalitis in humans and most other mammals. It remains one of the most common viral causes of mortality in the developing world.

Objective: The aim of this study was to determine the factors that affect compliance of pediatric patients advised to receive rabies Post-exposure Prophylaxis (PEP).

Methods: Pediatric patients zero months to 18 years old who were bitten by animals and thereafter sought consult from January to March 2009. Subjects with Category II and III exposure bites and advised PEP, who have telephone contact numbers, and gave verbal consent to participate were included. Excluded subjects were those who cannot be accessed by telephone or mobile, had previous animal bite and had received prior rabies immunization. Data were gathered through chart review and telephone interviews. Total number of patients who complied and did not comply with PEP and the factors related to compliance were determined.

Results: One thousand two hundred forty three pediatric patients sought consult and were advised to receive PEP: 757 (61%) were males and 496 (39%) were females. Most common age group was 2-to-5 yrs (41%), followed by 6-to-10 years (32%). A higher proportion of females were noted under Category II exposure while a higher proportion of males were noted under Category III. Most common biting animal was dog. The highest proportion of subjects with multiple body bites were from the very young age group (0 to 1 year old). Most commonly injured body parts were the upper extremities (32.7%), lower extremities (42.7%) and head (16%). The two-site intradermal (ID) rabies vaccine regimen was prescribed on days 0, 3, 7 and 30; however, there was a declining trend in rabies vaccine and rabies immune globulin (RIG) received. Compliance rate of RIG (55%) and rabies vaccine (31%) were low. Factors affecting compliance to rabies PEP were: 1) fear of acquiring rabies and knowledge of the gravity of the disease; 2) vaccine cost and affordability; and 3) knowledge on status of biting animal.

Conclusion: The most salient issue in rabies PEP compliance is the affordability of the vaccine.

INTRODUCTION

According to WHO World Survey of Rabies¹, in 2004, the Philippines ranked 6th with 248 deaths due to rabies (with India still at 1st place). Modern cell culture vaccines including purified vero cell rabies vaccine (PVRV) and purified chick embryo cell rabies vaccine (PCECV) are currently being used for PEP in the Philippines². Two economical reduced-dosed intradermal regimens of tissue-culture rabies vaccine recommended by the WHO had been used. They were less expensive than the intramuscular regimen and were safe and cost-effective³. These regimens had tremendous cost-saving implications for rabies PEP regimens, particularly for centers where large numbers of bite victims are seen daily⁴.

In the Philippines, rabies continues to cause human suffering and death. The incidence of human rabies deaths in the country is one of the highest reported worldwide at three per one million population. Approximately, of the 400,000 people who sought consult for rabies exposure annually, 75% would require PEP^{5,6}. However, only about 65% would receive it, and a smaller fraction of this percentage would actually complete it. Since there is no established, specific treatment for rabies once symptoms have begun, emphasis on patient education and compliance to PEP should be paramount.

The Anti-Rabies Act of 2007 (RA no. 9482) mandates the implementation of a program to control and prevent human and animal rabies.⁷ Part of this program is the provision of PEP to bite victims. Compliance to PEP is emphasized because cases of human rabies may occur due to poor wound care, incorrect administration of rabies vaccine and/or RIG, incomplete regimens, delayed treatment or when exposures go unrecognized and PEP is not sought. This study aims to determine and analyze the factors affecting patient's compliance to PEP as well as the health outcomes of patients. It is hoped that the results will be helpful in the development of educational materials and will strengthen the

government's advocacy for rabies control and eradication.

MATERIALS AND METHODS

This cross sectional study included pediatric patients (18 years and below) who sought consult at the Research Institute for Tropical Medicine (RITM) for animal bites from January to March 2009 and were advised to receive PEP.

Included were subjects who fulfilled the criteria for WHO category II and III exposure and were advised to receive rabies PEP; had contact numbers easily accessible via landline or mobile number; and had given verbal consent to participate in the study.

Excluded were those who cannot be accessed or contacted through telephone or mobile number, had a history of previous bite or had received prior rabies immunization since such patients are advised to receive boosters instead.

This study was approved by the Institutional Review Board of both RITM and Philippine Children's Medical Center (PCMC). A verbal consent was obtained from the patient or parents/guardians of children prior to follow up interview. Subjects' records and data (patient's age, sex, contact numbers, nature of animal bite exposure, source of bite, status of biting animal, type of vaccine regimen advised, number of vaccine doses given, location of hospital or animal bite where PEP was completed) were retrieved from the RITM's Animal Bite Registry and Medical Records Department. Category of bite was determined by attending physician. Follow-ups with regard to the date of a subject's exposure and compliance with the scheduled PEP were made based on the patient's record/chart; also, follow-up through telephone was done by the investigator. The total number of patients who complied and did not comply with the PEP was determined based on patients' records. Those who did not have a record of PEP completion were followed-up through telephone by the investigator. Subjects who were contacted

were divided to: 1) those who complied; and 2) those who were not able to comply. Factors affecting compliance to the advised PEP regimen between the two groups were evaluated with regard to vaccine costs (actual cost of recommended PEP and affordability of patient/parents), location of hospital or animal bite center, distance of hospital or animal bite center (if easily accessible in terms of kilometers, or if the patient could not determine exact distance, whether how many hours by travel or if the patients commutes, how many does he/she takes to get to the hospital and how much its travel fare costs them), travel time, and parents' knowledge regarding gravity of rabies disease and importance of PEP. Clinical outcome was assessed based on the presence or absence of symptoms five-to-seven months after the patients had completed PEP.

Data Analysis

The distribution and cumulative number of pediatric patients seen and advised rabies PEP for the period of January to March 2009 were investigated. Frequencies were calculated for the categorical variables. The variables taken into account were: 1) patient's demographic profiles such as age and sex; 2) exposure characteristics such as category of exposure, site of lesion, number of lesion (single or multiple); 3) status of biting animal; 4) treatment such as type and route of drugs (rabies vaccine and/or immunoglobulin), number of doses prescribed, number of doses administered; and 5) factors affecting compliance of treatment.

RESULTS

A total of 1,243 pediatric patients sought consult and were advised PEP from January to March 2009: 757 (61%) were males and 496 (39%) were females. Among the subjects, the most common age group was from 2-5 years (41%), followed by 6-10 years (32%). Peak of ages for both sexes were 2-10 years old with slight increases in extreme ages (0-1 years old and 15-18 years old) among females. The

proportion of males and females aged 11-14 years was similar. As to the nature of exposure of animal bite, 913 (74%) had category III exposure while only 26% had category II exposure (Table 1).

Table 1. Demographics and Category of exposure of patients bitten

	Male (%)	Female (%)	Total
Age (Years)			
0mos – 1	6 (1)	11 (4)	17 (1)
2 – 5	323 (43)	185 (37)	508 (41)
6 – 10	252 (33)	143 (29)	395 (32)
11 – 14	99 (13)	63 (13)	162 (13)
15 – 18	77 (10)	84 (17)	161 (31)
Total	757 (61)	496 (39)	1,243 (100)
Nature of exposure			
Category III	571 (75)	342 (70)	913 (74)
Category II	186 (25)	144 (30)	330 (26)
Total	757 (61)	486 (39)	1,243 (100)

The most common biting animal was the dog which comprised 1,066 or 86% of all bites; 167 patients were bitten by cat (13%) and 10 patients were bitten by monkey (1%).

A total of 1,163 patients or 94% had a single body site location of the bite while 6% had bites in multiple sites. The distribution of the site of wounds by age is significant. Specifically, the highest proportion of subjects with multiple body bites is among the 0-1 year olds.

The most common involved body parts were those of the upper extremities (32.7%), lower extremities (42.7%) and the head (16%). The lower extremity was the most common site of the bite among all age groups. (Table 2) Upon follow-up investigation, 1,107 (89%) of the biting animals were observed for 14 days and were reported healthy, 84 (7%) were stray or had unknown outcome and 51 (4%) died or were killed; of the 51, only 3 were sent for rabies virus determination and 1 proved to be rabid. No laboratory determination was reported on the rest of the biting animals.

Table 2. Site and body part of bite wounds involved by age.

	0-1 yr (%)	2-5yrs (%)	6-10yrs (%)	11-14yrs (%)	15-18yrs (%)	Total
Site of Wound						
Single body site	48 (84)	445 (92)	361 (95)	157 (95)	152 (96)	1,163 (94)
Multiple body sites	9 (16)	37 (8)	19 (5)	9 (5)	6 (4)	80 (6)
Total	57 (6)	482 (39)	380 (31)	166 (13)	158 (13)	1,243
Body Part Involved						
Head	14 (24)	111 (22)	49 (12)	16 (10)	10 (7)	200
Upper extremity	23 (40)	178 (36)	127 (32)	43 (27)	42 (27)	413
Lower extremity	20 (34)	165 (33)	169 (43)	90 (57)	94 (62)	538
Trunk	1(2)	35 (7)	36 (9)	9 (5)	3 (2)	84
Buttocks	0	8 (2)	13 (4)	1 (1)	3 (2)	25
Total	58	497	394	159	152	1,260

Out of the 1,243 patients who were advised to get PEP, only one patient opted to receive and had completed the intramuscular (IM) regimen of PVRV. The rest of the patients received the two-site intradermal (ID) regimen on days 0, 3, 7 and 30. The patients received either PVRV (Verorab) or PCEC (Rabipur). Upon first consult and advised on PEP, 1,243 (100%) had received the day 0 dose. On days 3, 7 and 30, a sequential decline was noted while on PEP (Table 3).

Table 3. Route of Rabies PEP Received

	Compliance to prescribed ID regimen Total	Compliance to prescribed IM regimen Total
Day 0	1,242 (100%)	1
Day 3	883 (71%)	1
Day 7	704 (57%)	1
Day 14	-	1
Day28/30	273 (22%)	1

Of the 671 patients prescribed with ERIG, only 414 (62%) complied and out of the 195 prescribed with HRIG, only 60 (31%) complied. Total compliance rate for RIG was 55%. Although a total of 913 patients were categorized as having bite category III which would require PEP of both RIG and rabies vaccine, 866 of the patients were only

prescribed with RIG. No record of RIG prescribed was noted on the remaining patients, which may be attributed to lost follow-up of these patients.

Table 4. Type of RIG prescribed and received.

	Number of patients prescribed at consult	Compliance to prescribed RIG
ERIG	671	414 (61.69%)
HRIG	195	60 (30.77%)
Total	866	474 (55%)

Data obtained during follow-up investigation

Of the 1,243 patients, 973 (78%) did not have any record of PEP completion based on the animal bite registry. Medical records of these patients were obtained and only 346 had contact numbers (mobile and landline numbers) on record. Among the 346 patients, 166 (17%) were reached and were able to give verbal consent. Of these 166, 121 (71%) had completed PEP and 45 did not.

Three-hundred thirty four patients (85%) had completed PEP at RITM; this included those patients already recorded in the animal bite registry and those who were followed-up through telephone. Only 61 (15%) patients had completed PEP in animal bite centers near their places of residence. Total compliance rate for rabies vaccine was 32%.

Of the 166 patients reached, 121 complied with PEP upon advice. Their primary and only reason was their knowledge on rabies and the gravity of its disease. Fear of acquiring rabies was their main motivator for completion of PEP. Among the 45 patients who did not complete the vaccination regimen, vaccine cost and affordability were the primary reasons (73%).

Table 4. Factors for compliance to PEP.

FACTORS	Complied (N=121)	Non-complied (N=45)
Vaccine cost (affordability of by patient/parents)	0	33 (73%)
Healthy status of biting animal	0	7 (16%)
Patient/parents' knowledge on gravity of rabies disease and importance of PEP	121 (100%)	5 (11%)

All these patients were healthy after five to seven months from date of the bite. Information on the survival and mortality on those who were not contacted was not obtained.

DISCUSSION

Rabies is a disease that is entirely preventable provided that complete PEP is implemented promptly⁵. Exposed children do not receive timely and complete PEP, and a much higher proportion of young children contract and die of unrecognized rabies than estimates from Asia suggest. The WHO recommended regimen of PEP for people bitten by rabid animals consists of a combination of wound cleaning, active immunization with a tissue culture rabies vaccine and passive immunization with equine (or, rarely, human) rabies immunoglobulin⁵; this has proved to be highly effective in preventing infection. Inclusion of rabies immunoglobulin in the post-exposure regimen is regarded as mandatory for

WHO category III exposures (bites or scratches that break the skin and contamination of mucosa with saliva) which constitute about 60% of all cases⁶. PEP may be discontinued if the animal involved is a dog or cat that remains healthy within the fourteen-day observation period² or if the animal is humanely killed and proven to be negative for rabies by a reliable diagnostic laboratory using a prescribed test. If the animal inflicting the wound is suspected of being rabid and is not apprehended, PEP should be administered immediately.

In this study, records of 1,243 pediatric patients advised and started on PEP at RITM during the period of 1st quarter (January to March) of 2009 were reviewed. Although the true extent of completion in all patients is unknown, of the 166 contacted and followed-up cases, 73% had completed PEP. Factors affecting compliance were 1) fear of acquiring rabies and knowledge on its disease gravity, 2) vaccine cost and affordability, and 3) knowledge on status of biting animal

RITM is one of the two major public rabies vaccination centers and has a catchment of more than 14 million people living in the Manila Metropolitan area and in four adjacent provinces. It has been providing intradermal (ID) PEP to its patients since 1995⁸. Animal bites, particularly dog bites, have been the number one reason for consultation at RITM for many years. Based on RITM's animal bite census⁹ for the year 2007, there was a total of 15,232 consults for animal bites. In 2008, the number increased to 33,718 bite consults (54.8%): 11,985 were dog bites (36%) and 2,945 (9%) were cat bites. Dog bite category III exposure accounted for 78.3% of consults, 20.4% for category II and 0.9% for category I; of these, 573 (1.7%) sought for consult for post-exposure prophylaxis and 38 (0.11%) consulted for pre-exposure prophylaxis⁹.

A three-pronged approach – dog immunization, responsible pet ownership and post-exposure prophylaxis – is still recommended for all government units to control rabies in their areas of responsibility¹⁰.

Animal bite exposures were seen predominantly among boys, almost twice (61%) when compared to girls (39%). Majority of these children belong to the 2-to-5 years and 6-to-10 years age group. However, a higher proportion of females were noted in the extreme of ages. Females were significantly more prone to have category II exposures, but increase in severity in category III were noted among males. Single bite was seen to be the most common in the areas of the upper and lower extremities. A higher proportion of patients who had multiple bite sites was seen in the extreme young age group (0-1 year of age). Young children are most vulnerable since they are smaller and would have a harder time to escape the animal. Proximity of the animal to the biting site of young children is explained by the frequency of bites located in the extremities. Most common biting animal is the dog, which correlates to the major vector of rabies here in the Philippines⁶.

There was a decrease in the number of patients receiving subsequent doses of rabies vaccine. All patients at first consult received the recommended day 0 or 1st vaccine dose. On subsequent days or 3, 7, and 30, a decrease in the receipt of vaccines was noted. These observations could be explained by either: 1) transfer of patients to other more accessible animal bite centers for continuation of rabies vaccine PEP; or 2) decrease in compliance to rabies vaccine PEP by the patient himself.

The compliance rate to rabies immunoglobulin (RIG) is low at 55%, considering that this is recommended for patients who sustained category III exposures. Human rabies immunoglobulin (HRIG) is indicated for a person with positive skin test to Equine rabies immunoglobulin (ERIG) or F(ab')₂ products; known history of hypersensitivity to equine sera; multiple, severe category III bites on head, neck, and face area, regardless of status of the biting animal; multiple, severe category III bites on other parts of the body by animals that are sick, suspected or proven to be rabid; symptomatic HIV patients; and for

newborns of pregnant rabid mothers⁶. However, HRIG is more expensive than ERIG although less adverse reactions may be noted. For example, for a 10-kg child with category III bite, the recommended dose of HRIG is 20 iu/kg, a preparation 150 iu/2ml vial costs PhP4, 290.00 (RITM price). The actual dose needed for the child is 200 IU which is approximately 1 ½ vial, amounting to PhP 6,435.00. In ERIG, recommended dose is 40 iu/kg, preparation is 200 iu/5ml vial (PhP 1,176.00); hence, the actual dose and amount is 400 IU (2vials) at PhP2, 352.00. All pediatric patients were seen and evaluated by the attending physician and importance of PEP adherence was extensively explained to the patients. Number of patients who complied and received RIG were low, hence economics played a role.

Among the 166 contacted, 121 (73%) complied with PEP. Gravity of rabies disease and importance of adherence to PEP were the primary reasons for compliance. Fear of acquiring the disease was the main motivator. During follow-up, the patients/parents had stated and understood well the explanation given to them upon their first consult, with regard the number of doses to complete, number of years PEP could be effective, schedule of booster doses, and strict observation for 14 days of the biting animal and the patient himself.

Forty-five (27%) of the contacted patients did not complete vaccination. Compliance rate to rabies vaccine was also low at 32%. Despite the accessibility of animal bite centers near the patients' residences, there was a higher proportion of patients who did not comply with the required PEP due to vaccine affordability (33/45, 73%). The ID vaccine regimen costs PhP420.00 per 2-ID dose. This consists of 0.1ml of rabies vaccine (either PCEC or PVRV) administered intradermally at 2 sites on days 0, 3, 7 and 30. It is proven efficacious, provides protection against contracting rabies, is safe and less expensive⁴. These were mostly noted on patients on days 3 and/or 7 doses. Other factors found to be related to compliance were:

1) knowing that the biting animal is still healthy and alive, hence, patients felt it “safe” not to continue PEP; 2) trauma of the child to the vaccination, thus, refusing to go back; and 3) the “bahala na” attitude, where patients would just leave it to fate with regards to the health outcome. The proportion of subjects who complied and cited their knowledge on rabies and its gravity is significantly higher than those who did not comply.

CONCLUSIONS

Based on this study, compliance rate for rabies PEP is low and the most salient issue is the affordability of the vaccine. There are still a few Filipinos who are ignorant and lack initiative of this grave yet preventable health problem.

RECOMMENDATIONS

Continuous education, government subsidy and implementation must always be emphasized for continued awareness about rabies prevention and prompt PEP administration. It is important to keep in mind that rabies vaccines are worthless they are not utilized. In reality, rabies is a shared problem that can only be tackled by a multidisciplinary approach. We highlighted the practical problems that face people exposed to animal bites, and their compliance to PEP, which can be alleviated given continuous partnership by the health and government sectors.

ACKNOWLEDGEMENTS

The author is extremely thankful to Dr. Jaime Santos, Head, Section of Pediatric Infectious Disease, Philippine Children’s Medical Center for his valuable support, and to Dr. Lucille Perez for her guidance and technical support. The author also expresses her sincerest gratitude to Dr. Beatrice Quiambao, and Dr. Nancy Bernal of the Research Institute for Tropical Medicine for their unflinching help and guidance.

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