Human rabies post exposure prophylaxis in Bhutan, 2005–2008: Trends and risk factors

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Abstract

The aim of this study was to understand the use and distribution of human rabies post exposure prophylaxis (PEP) vaccine in Bhutan and to identify risk factors for receiving an incomplete course of the vaccine. We analysed post exposure treatment records from 28 medical hospitals from 2005 to 2008. Males (59%) accounted for significantly more PEP events than females (41%) across all age groups ($P < 0.001$). Children–particularly 5–9 years of age – received more rabies PEP than other age groups. Animal bite and non-bite accounted for 27% (n = 2239) and 16% (n = 1303) of rabies PEP, respectively, whilst 57% (n = 4773) of the PEP events had no recorded information about the reasons for post exposure treatment. Post exposure treatment was provided throughout the year with a higher number during the winter and spring months. The number of PEP events significantly ($P < 0.001$) increased between 2005 and 2008, from <1000 to >2800 events, respectively. Significantly ($P < 0.001$) more PEP events were reported from the southern parts of Bhutan that are endemic for rabies or those areas in eastern Bhutan that have reported rabies outbreaks than other parts of Bhutan. Forty percent (n = 3360) of the patients received an incomplete course of vaccine (<5-doses of vaccine intramuscular). Results suggest that patients with animal bite injury were less likely to receive an incomplete vaccine course than non-bite recipients, and patients presented to hospitals in rabies endemic or outbreak areas were less likely to receive an incomplete course than in non-rabies areas or rabies free areas. Similarly, patients presenting to hospitals for PEP during spring and summers months were less likely to receive an incomplete vaccine course than those during other seasons. Public education campaigns need to be conducted in Bhutan to reduce dog bite incidents and also to prevent mass exposures to rabies. A thorough assessment of each individual case based on the WHO guidelines would reduce unnecessary PEP (and therefore costs) in Bhutan.

1. Introduction

Rabies remains a significant public health problem in the world, with an estimated 55 000 human deaths occurring each year, mainly in developing countries of Asia and Africa (Knobel et al., 2005). Although rabies is inevitably fatal once clinical symptoms develop, the disease is preventable with timely treatment following an exposure to a rabid animal. The recommended post-exposure treatment consists of a thorough washing or flushing of the bite wound with soap and water or with viricidal agents, administration of rabies vaccine and infiltration of rabies immunoglobulin into and around the bite wound (WHO, 1996; WHO, 2010a). The main aim of post exposure prophylaxis (PEP) is to neutralize or inactivate inoculated virus in the wound before it can enter the nervous system of the patient (Warrel 2004). Therefore, a quick decision – based on a thorough assessment of the risk – must be made by the physician about whether to initiate rabies PEP. Post exposure prophylaxis is unnecessary and is a waste of resources if the biting animal is not rabid. As per the recent estimates of the World Health Organization (WHO), ≥15 million people receive PEP for rabies worldwide each year, mostly in India and China (WHO, 2010a). Children are at the greatest risk of rabies exposures and approximately 40% of PEP is given to children aged 5–14 years old (WHO, 2010a).

In Bhutan, rabies in animals is mainly prevalent in the southern districts that border India. Between 1996 and 2009, 814 cases of rabies were reported in dogs and other domestic animals in Bhutan (Tenzin et al., 2011). Similarly, from January 2006 to January 2011, nine human rabies deaths have been reported (eight cases in southern Bhutan and one in eastern Bhutan, 1.2/100000 population at-risk) (MoH, 2010; Kuensel 2009a; Kuensel 2010a; BBS, 2011). Because of the frequent outbreaks of rabies in dogs and farm animals in southern Bhutan, medical hospitals in all regions provide rabies PEP free of charge to those who have been bitten by animals (category II and III exposure) and also for category I exposure (touching/feeding animals, licks on intact skin) or for ingestion of meat and dairy products derived from suspected rabid animals. Currently, the human diploid cell vaccine (HDCV) is used and treatment follows the standard 5-dose (1 ml each) intramuscular administration regimen (Essen regimen) on days 0, 3, 7, 14 and 28 (WHO, 2010a). Although the number of human rabies cases in Bhutan is low and sporadic, the number of persons seeking rabies PEP is increasing because of the large number of stray and free-roaming dogs and increased incidents of dog bite, and because of mass exposures (likely category I exposure) during periods of rabies outbreaks in animals (BBS, 2010, Bhutan Observer 2010; Kuensel 2009b). However, little is known about the epidemiologic characteristics of rabies PEP use in Bhutan.

In this study, we explored the epidemiology of human rabies PEP use based on treatment records between January 2005 and December 2008 from 28 selected hospitals and Basic Health Units, in Bhutan. The aim of this study was to describe the use and distribution of human rabies post exposure prophylaxis in Bhutan and to identify risk factors for an incomplete course of PEP. The results from this report are intended to assist medical practitioners and public health policy makers to reduce the incidences of human exposures and prioritizing the use of PEP based on the WHO guidelines. This is also likely to improve the national surveillance for rabies post exposure prophylaxis in Bhutan.

2. Materials and methods

2.1. Data sources

Bhutan is administratively divided into 20 districts and 205 subdistricts and has a population of about 0.68 million (NSB, 2005). There are 30 medical hospitals, 181 Basic Health Units (BHUs) and 38 indigenous medicine units, distributed in the districts and sub-districts in the country (MoH, 2010).

Human animal bites are not a reportable condition in Bhutan, but bite victims visit hospitals for treatment and medical advice. Post exposure rabies prophylaxis vaccine is mainly provided via hospitals, but is also given at some of the BHUs located in rabies endemic areas or during rabies outbreaks. These hospitals and BHUs record basic information about patients provided with post exposure prophylaxis. For our analysis, we acquired PEP case data from 18 hospitals and 10 BHUs in Bhutan for the period January 2005 to December 2008. There was no PEP record (no data) in five of the civilian hospitals contacted. The PEP data from the remaining seven hospitals were not included due to logistic reasons of data collection (five military hospitals and two civilian hospitals). Similarly, majority of the BHUs were not considered for data collection due to logistic reason (remote location and also absence of rabies cases in those areas, assuming no PEP course would have been given). Only sampled BHUs from rabies endemic/outbreak areas were included for our analysis. There was no reporting system of PEP data (especially individual case) to the main data management unit in the Health Ministry in Bhutan from the respective health centers and was difficult to access this information. Available information that we collected included demographic data (age and gender of victims), mode of contact and circumstances of exposure, date of patient presentation to the hospital or BHU and date of administration of PEP. The study was approved by the Ethics Committee of the Human Research and Epidemiology Unit, Ministry of Health, Bhutan.

2.2. Data analysis

The data were entered into a Microsoft Excel spreadsheet (Microsoft Excel, Redmond, WA). Descriptive analyses of the data were performed using Microsoft Excel. Chi-square tests were used to compare the difference in proportions of PEP recipients between gender, age groups, season and years. To make meaningful comparisons between age groups, observed frequencies of PEP for various age groups were compared with expected frequencies calculated from the Bhutan census data of 2005 (NSB, 2005). For comparing gender, seasonal and annual differences, equal expected frequencies were assumed between groups. A P-value of <0.05 was considered statistically significant.

Although the complete course schedule of post exposure prophylaxis (Essen regimen) is five doses (WHO, 2010a), many patients received an incomplete course of the vaccine (i.e. <5 doses). We conducted logistic regression analyses (GenStat Version 11.1 (VSN International Ltd., UK) to identify possible risk factors for incomplete PEP as the outcome variable (incomplete versus complete). The risk factors investigated included age group, gender, type of exposure (animal bite versus non-bite), rabies risk area (rabies outbreak or endemic area versus non-outbreak or free areas), season and year. Initially, we constructed contingency tables between explanatory variables and the outcome, calculated unadjusted odds ratios (OR) and the corresponding 95% confidence intervals and P-values. The variables that had a significant crude association with the outcome ($P < 0.25$) were selected for multivariable logistic regression model, using a forward stepwise selection approach. The selected variables were examined for collinearity in pairs by calculating Spearman's rank correlation coefficient (ρ) and no highly correlated pairs of variables ($\rho > |0.70|$) were observed and all variables were retained for further analysis. Variables with P-values <0.05 (based on the likelihood-ratio chi-squared test) in the multivariable model were considered to be significantly associated with incomplete PEP. Model diagnostics were checked by examining the standardised Pearson residuals, leverage values, and delta betas (Dohoo et al., 2009). To control for effects of clustering of observations from the same hospitals (and BHUs), we refitted the final model using a generalized linear mixed model by adding hospitals as a random effect term. Intra-class correlation (ICC) was calculated for the random effect term using the latent variable approach (Dohoo et al., 2009).

A Geographic Information System (ArcGIS 9.3, ESRI, Redland, CA, USA) was used to illustrate the distributions of human rabies post exposure prophylaxis given in different hospitals and BHUs in Bhutan. Here, the total number of patients that were given PEP in each selected hospital/BHU was mapped and represented by proportional symbols for visualization and for understanding the geographic distribution of PEP.

3. Results

Data were collected from a total of 9084 patients from 18 hospitals and 10 Basic Health Units in Bhutan. Data for pre exposure prophylaxis (117 cases) were excluded from the analysis because the aim of the study was to understand the use and distribution of post exposure prophylaxis only. Of the 8967 PEP events, 8315 (92.7%) patients were given various courses of rabies post exposure prophylaxis, 504 patients were given tetanus toxoid injection, and there was no information about the type of treatment provided in the remaining 148 patients. Thus for the analyses reported in this paper, we used a dataset of 8315 patients that were given PEP.

3.1. Gender

A total of 8302 patients (99.8%) had complete information for gender. Of these, 58.6% (n = 4864) were male and 41.4% (n = 3438) female. The proportion of rabies PEP recipients was significantly higher in males than females during the study period ($\chi 2 = 277$; $P < 0.001$).

3.2. Age

Of the 8315 patients that received PEP, age was not recorded for 208 patients. The median age of patients receiving PEP was 21 years (range <1 to 96 years) and the modal age was 8 years. The observed and the expected frequencies of PEP recipients differed significantly across age groups ($\chi^2 = 320$; $P < 0.001$). The majority (n = 5438, 67.8%) of the patients that received PEP were below 30 years of age, and the maximum number of cases was observed in the 5–9 years (n = 1235; 15.2%) and then the 10–14 years (n = 1049; 12.9%) age groups. Figure 1 illustrates the distribution of rabies PEP by age and gender between 2005 and 2008 in Bhutan, in which the proportion of PEP recipients in males was significantly higher than females across all age groups.

3.3. Seasonal and annual trend of post exposure prophylaxis

Data on date of PEP administration were available for 8187 patients. The first date (day 0) of the 5-dose vaccine course was used to examine the seasonal pattern. Post exposure prophylaxis were given throughout the year, but more were provided during the winter (n = 2367; 28.9%) and spring (n = 2256, 27.6%) months (Figure 2). The overall proportion of vaccine recipients across seasons was significantly different ($\chi^2 = 156$; $P < 0.001$). The proportion of PEP across each season in each year was also significantly different compared to that expected ($P < 0.001$). The number of patients that received PEP increased from <1000 patients in 2005 to >2800 patients in 2008 ($\chi^2 = 1059$; $P < 0.001$).

3.4. Mode of contact and type of exposures

Both animal bite and non-bite incidents were presented to the hospitals and BHUs for post exposure prophylaxis. The majority (n = 4773; 57.4%) of the PEP case records did not have information about the reasons for PEP (data not recorded in the treatment register); 26.9% (n = 2239) were given PEP because of animal bites and 15.7% (n = 1303) for non-bite incidents. The non-bite incidents mainly included category I exposure (touching and feeding of animals) and also ingestion of meat and dairy products derived from rabid animals. The details of the various reasons for PEP are illustrated in Table 1.

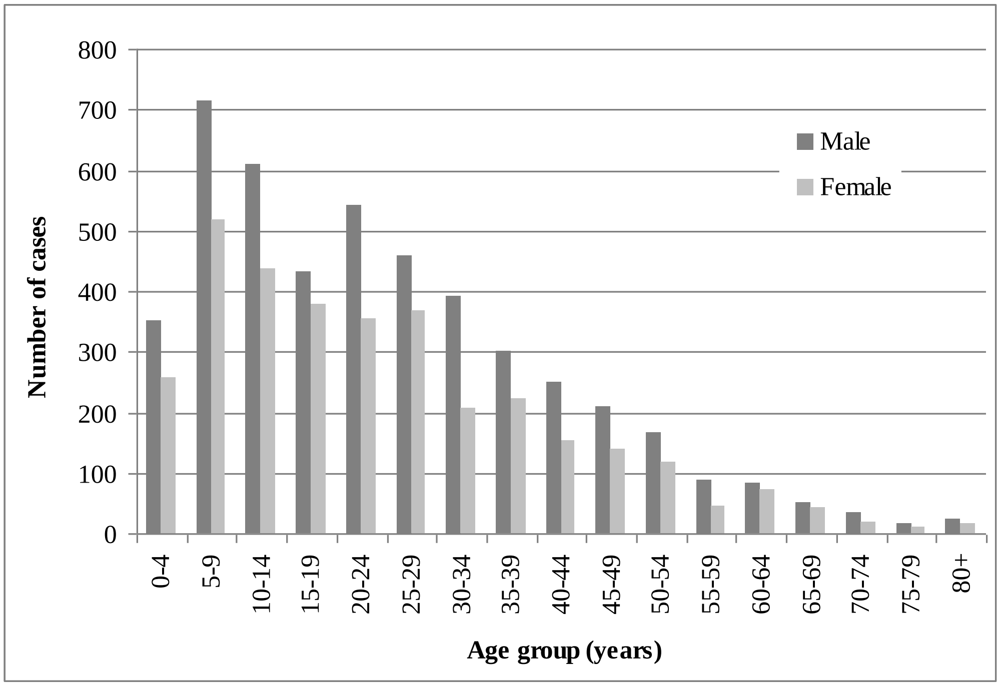

Figure 1: Distribution of rabies post exposure prophylaxis in people by age and gender in Bhutan from 2005 to 2008.

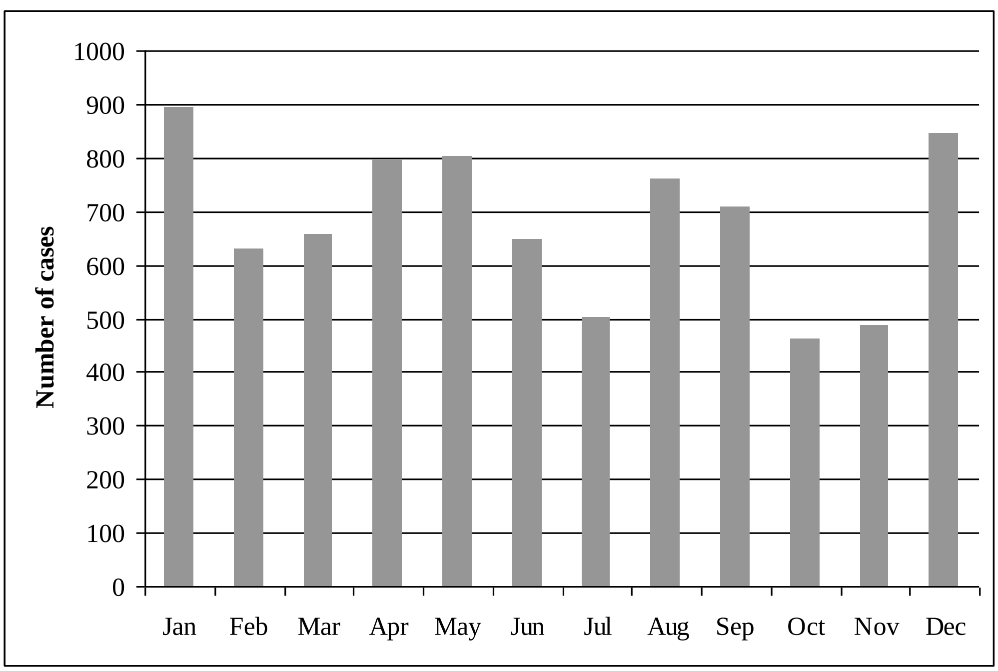

Figure 2: Monthly pattern of human rabies post exposure prophylaxis in Bhutan, 2005–2008.

Table 1: Descriptive statistics for mode of (likely) exposure and reasons for receiving rabies post exposure prophylaxis by people in Bhutan for a study period 2005 to 2008.

Reasons for PEP rabies vaccination	Number of PEP rabies vaccine given	% of PEP given
Dog bite	2099	25.24
Cat bite	71	0.85
Cat scratches	16	0.19
Rat bite	43	0.52
Other animal bite (monkey, bear, horse, goat, pig)	10	0.12
Contact with rabies patient	135	1.62
Contact/handled rabid cattle (feeding, touching and handling of carcasses during zoo sanitary measures)	234	2.81
Contact/handled rabid dog (during zoosanitary measures)	142	1.71
Dairy product consumption (milk, butter, cheese) derived from rabid or rabies suspected cow	607	7.30
Meat consumption (meat derived from rabid or rabies suspected cattle)	156	1.88
Other mode of contacts	29	0.35
Missing information	4773	57.40
Total	8315	100

3.5. Patterns of post exposure prophylaxis due to dog bites

Of the animal bite incidents, dog bites formed a major (93.7%) component of PEP in humans. Of the 2099 dog bite incidents in humans, 59.4% (n = 1243) of patients were male and 40.6% (n = 849) female, and the difference between the gender was significant ($\chi^2 = 74.20$; $P < 0.001$). The majority of the PEP due to dog bite was reported in children, especially within the age group of 5–14 years. The proportions of observed and expected PEP in humans due to dog bite were significantly different across age groups ($\chi^2 = 98.44$; $P < 0.001$). Figure 3 illustrates the age and sex distribution of PEP due to dog bites. It indicates that males received more PEP than females across all age groups due to dog bites in Bhutan. Dog bites were reported throughout the year, but more were reported in the spring months. The difference between the observed and expected cases was significant across all seasons ($\chi^2 = 22.17$; $P < 0.001$).

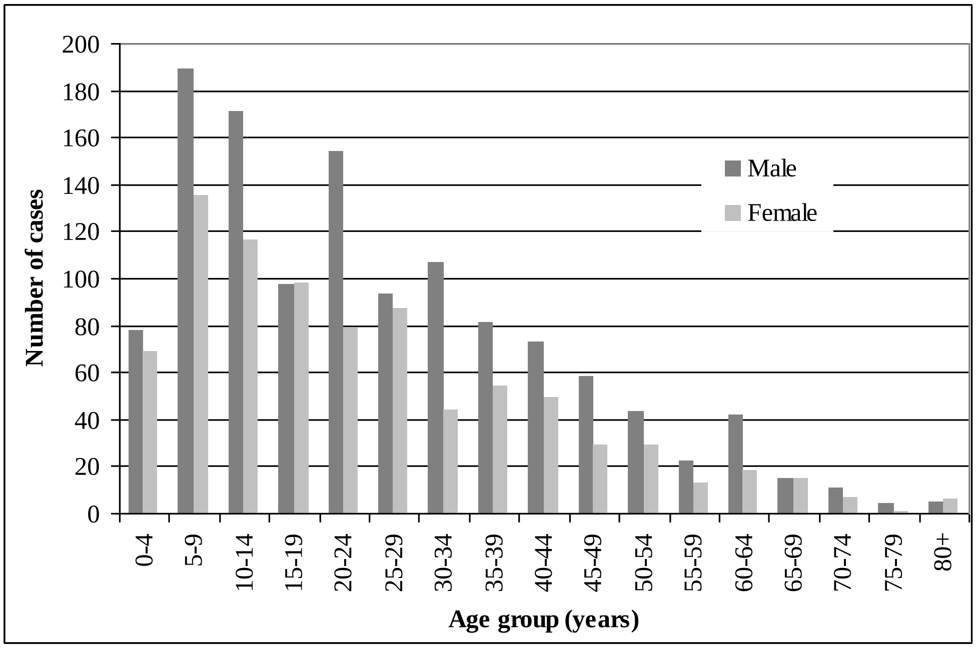

Figure 3: Distribution of dog bite victims classified by age and gender who received rabies post exposure prophylaxis in Bhutan, 2005–2008.

3.6. Rabies post exposure prophylaxis course

Of the patients receiving rabies PEP, 3859 (46.4%) received the standard 5-dose intramuscular injection (Essen regimen) on day 0, 3, 7, 14 and 28; 1096 (13.2%) patients received a 6-dose course (including day 90); 705 (8.5%) patients received a 4-dose course; 1337 (16.1%) patients received a 3-dose course; 551 (6.6%) patients received a 2-dose course; and 767 (9.2%) patients received only 1-dose of the vaccine. Overall, 3360 (40.4%) patients received an incomplete course of the vaccine (<5-dose course) based on the Essen regimen. Of the 3360 incomplete vaccine course recipients, 18.8% (n = 631) of the patients had animal bite injuries, 15.5% (n = 520) of the patients had non-bite incidents, and there was no information about the type of exposures for the remaining 2209 (65.7%) patients.

3.6.1. Risk factors for incomplete PEP course

Five variables (Table 2) were unconditionally associated ($P < 0.001$) with having an incomplete PEP vaccine course – age, type of exposure (animal bite versus non-bite), rabies risk area (rabies outbreak/endemic versus non-outbreak/free area), season and year. Gender was not associated with an incomplete PEP course ($P = 0.499$). Except for the type of exposure variable (due to much missing data) and the gender, all other variables were included in the multivariable model. Patients that presented to hospitals in rabies endemic or rabies outbreak areas were more likely to complete the vaccine course than patients in non-rabies risk areas. Compared to 0–14 years, other age groups were more likely to have an incomplete vaccine course; patients that visited a hospital for PEP during winter and autumn months were more likely to have an incomplete vaccine course than in spring and summer months. The proportion of incomplete course of vaccine recipients significantly increased over the study years (2006 through 2008). Table 3 illustrates the final generalized linear mixed model in which the hospital was included as a random effect in the model. Coefficients for all variables were almost similar to that of the unadjusted multivariable model except for area (rabies outbreak or endemic area versus non-outbreak or free areas) which became non-significant in the model adjusted for clustering. The estimated intra-class correlation (ICC) in the final model was 0.63, indicating that a greater proportion of total variation was clustered at the hospital level. Examination of the residuals showed no evidence of unusual influence of any observation on the model predictions.

3.7. Spatial distribution of post exposure prophylaxis

The distribution of the total number of patients given rabies PEP in different hospitals (and BHUs) in Bhutan is shown in Figure 4. The map illustrates an unequal distribution of PEP patients among the hospitals. As expected, hospitals located in areas of southern Bhutan that are endemic for rabies and those hospitals with catchment areas covering reported rabies outbreaks during the study period (e.g. eastern Bhutan) had given significantly more (χ^2 = 1847, P < 0.001) PEP (n = 6117, 73.57%) compared to hospitals located in the interior of Bhutan that did not report rabies (n = 2198, 26.43%). Within the interior parts of Bhutan, some of the hospitals located in western Bhutan (e.g. Thimphu and Paro) that have no history of presence of rabies for at least 18 years had provided a large number of rabies PEP to patients (see Figure 4).

Table 2: Contingency table for explanatory variables with incomplete rabies post-exposure prophylaxis in Bhutan, 2005 to 2008, and odd ratios based on univariable logistic regression analysis.

Variables/categories	**Incomplete**	**Complete**	**OR**	**95% CI**	**P-value[a]**
Age group					<0.001
0–14	1012	1893	1.00	-	
15–29	1095	1438	1.42	1.27–1.59	
30–44	609	918	1.30	1.14–1.47	
> 45	456	686	1.23	1.07–1.41	
Gender					0.499
Female	1403	2035	1.00	-	
Male	1949	2915	0.97	0.88–1.06	
Type of (likely) exposure (animal bite vs. non bite)					<0.001
No	520	631	1.00	-	
Yes	783	1608	0.59	0.51–0.68	
Rabies outbreak/risk areas					<0.001
No	1452	1908	1.00	-	
Yes	746	4209	0.23	0.21–0.26	
Season of PEP					<0.001
Winter (Dec–Feb)	1041	1326	1.00	-	
Spring (Mar–May)	865	1391	0.79	0.67–0.91	
Summer (Jun–Aug)	637	1273	0.63	0.51–0.76	
Autumn (Sep–Nov)	762	892	1.08	0.96–1.21	
Year					<0.001
2005	238	641	1.00	-	
2006	846	1206	1.88	1.59–2.24	

2007	1139	1623	1.89	1.59–2.23	
2008	1137	1485	2.06	1.74–2.44	

[a] P-value based on likelihood ratio chi-square test of significance.

Table 3: Final generalized linear mixed logistic model with hospitals added as random effect for incomplete rabies post exposure prophylaxis course in Bhutan for the study period 2005 to 2008

Variables/categories	***b***	***s.e (b)***	**OR**	**95% CI**	**P-value [a]**
Hospital-level random effect	5.78	2.45	-	-	-
Constant	0.17	1.02	-	-	-
Age group					
0–14	-	-	1.00	-	
15–29	0.24	0.06	1.27	1.12–1.44	<0.001
30–44	0.26	0.07	1.29	1.11–1.49	
> 45	0.20	0.08	1.22	1.04–1.43	
Rabies outbreak/risk areas					0.287
No	-	-	1.00	-	
Yes	-1.26	1.18	0.28	0.03–2.89	
Season of PEP					<0.001
Winter (Dec-Feb)	-	-	1.00	-	
Spring (Mar-May)	-0.24	0.07	0.78	0.67–0.90	
Summer (Jun-Aug)	-0.39	0.07	0.67	0.57–0.78	
Autumn (Sep-Nov)	0.06	0.07	1.06	0.91–1.23	
Year					<0.001
2005	-	-	1.00	-	
2006	0.30	0.11	1.35	1.08–1.69	
2007	0.32	0.10	1.37	1.12–1.69	
2008	0.23	1.02	1.96	1.59–2.42	

[a] P-value based on likelihood ratio χ^2 test of significance.

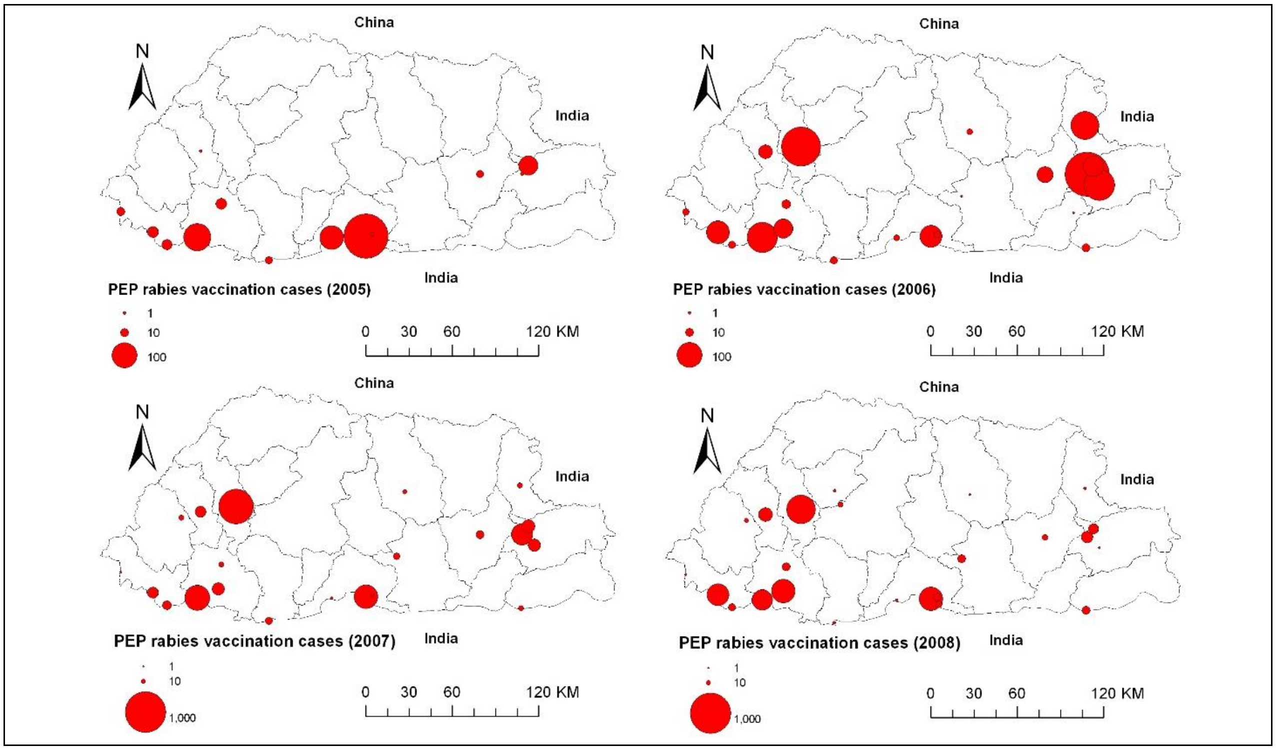

Figure 4: A district map of Bhutan showing the total number of persons (shown as proportional symbol) that were given rabies post exposure prophylaxis in different hospitals between 2005 and 2008.

4. Discussion

This report describes human rabies exposure and post exposure prophylaxis in Bhutan from 2005 to 2008. Our study showed that the overall prevalence of PEP was higher for children, especially for those up to 14 years of age, and then the trend decreased as age increased (Figure 1). This is in agreement with several other studies (WHO, 2010a; Martin et al., 1969; Helmick 1983; Pancharoen et al., 2001; Sriaroon et al., 2006, Blanton et al., 2005; Edison et al., 2010; Wyatt et al., 1999). It has also been suggested that animal bites in children are more likely to be reported to hospitals for wound treatment and possible vaccination because of parental concern (Martin et al., 1969). However, rabies experts from the Asian countries believe that children are at high risk of exposure to rabies, but less likely to report animal exposure, such as scratches or licks from dogs and cats, to their parents (Dodet, 2010). In this study, dog bite incidents were also more common in children than adults (Figure 9.3) suggesting that children received higher PEP than adults. We also identified that dog bites and PEP are significantly greater in males than females across all age groups (Figures 2 and 3), a finding observed in other studies (Martin et al., 1969; Helmick 1983; Wyatt et al., 1999; Khokhar et al., 2003; O'Bell et al., 2006)

Post exposure treatment was provided throughout the year in Bhutan, with higher number in the winter and spring months (Figure 2). This may be associated with increased dog bite incidents and also mass exposure (likely category I exposure) to rabies outbreaks occurring during these seasons. A previous study revealed a significantly higher number of rabies cases in animals during late winter through to the summer months in Bhutan (based on data from 1996 to 2009) (Tenzin et al., 2011), and it is likely that more PEP would have been given during these months. However, PEP data from 1996 to 2004 were not analyzed (data not available) to determine if a correlation exists between the number of PEP events and the seasons. A trend in PEP administration is evident, with the number of cases increasing from <1000 in the year 2005 to >2800 cases in 2008. This suggests that the number of PEP events is associated with the increased incidence of rabies outbreaks and also dog bite incidents (BBS, 2010; Kuensel, 2007). For instance, mass anti-rabies vaccination of people (n > 900) was implemented at the time of a major rabies outbreak in eastern Bhutan from 2005 to 2007 (Tenzin et al., 2010a) and in south-west Bhutan (n > 600) during 2008 (Tenzin et al., 2010b), following contact with rabid animals (likely category I exposure) or ingestion of meat and dairy products derived from rabid animals resulting in increased post exposure treatment over this period. Similarly, other studies in the US have observed more post exposure treatment during summer or warmer months, which is usually associated with increased animal exposure (e.g. dog bite) (Helmick 1983; Blanton et al., 2005; Wyatt et al., 1999; O'Bell et al., 2006)..

Although the recommended PEP regimen may differ based on the category of exposures and the prior history of immunization (WHO, 2010a), we found no reports of rabies immunoglobulin being regularly administered to dog bite victims in Bhutan. This may be due to the high cost of the biological and limited supply in the market (Warrell 2004; Wilde et al., 2005; WHO, 2010a). Although many lives may have been saved by using rabies vaccine alone, there are published reports of PEP failures in the absence of rabies immunoglobulin and when PEP administration methods had deviated from recommended PEP protocols (Shill et al., 1987; Wilde et al., 1989; WHO, 1995; Wilde et al., 1996; Gacouin et al., 1999; Sriaroon et al., 2003; Matha and Salunke 2005; Wilde 2007; Rupprecht et al., 2009) or occurred as true failure even when correct post exposure treatment protocol have been followed (Hemachudha et al., 1999; Wilde et al., 2005; Shantavasinkul et al., 2010). Considering the prevalence of rabies in domestic dogs in the border towns of southern Bhutan, it is imperative that the human rabies immunoglobulin (HRIG) (or less expensive equine rabies immunoglobulin (ERIG) or $F(ab)^2$ products of equine rabies immunoglobulin) (Quiambao et al., 2008) be administered to proven rabid dog bite cases (WHO category III exposure) in southern Bhutan, along with rabies vaccine and proper wound treatment (WHO, 2010a).

The rabies post exposure treatment is a complex decision making process for clinicians, especially in a country where there are large numbers of stray and free-roaming dogs, when the biting animal is not available for observation, where no quarantine of biting animals is practiced and laboratory testing is not normally done (McCombie 1989 ; Sriaroon et al., 2005)

Our study indicates that a large amount of rabies PEP is administered to patients whose risk of exposure to rabies virus is low (or non-existent) based on the WHO guidelines for post exposures prophylaxis (WHO, 2010a). It is also likely that the majority of people who were administered PEP for dog bites may in fact have been bitten by normal healthy dogs/pet dogs, and the anti-rabies vaccine may have been provided as a precautionary measure either due to pressure from the victims or the physician on duty cannot take the risk (Kuensel 2007; McCombie, 1989). We also found that approximately 16% of PEP was given to people with non-bite incidents, including touching and feeding of suspected/confirmed rabid animals, and ingestion of meat and dairy products (milk, butter, cheese) derived from suspected or confirmed rabid cattle. As per the WHO guidelines (WHO, 2010a), this entire group falls under category I exposure and no treatment is required. WHO guidelines clearly state that ingestion of raw meat or other tissues from animals infected with rabies is not a source of human infection (WHO, 2010a; 2010b). Although there have been no well-documented reports of human rabies transmission through such non-bite incidents (WHO, 2010a; Warrell 2004; ProMED-mail 2010), we believe that the PEP may have been administered by the clinician on duty because of the heightened concerns and anxiety of the people rather than in response to a true exposure (Blanton et al., 2005; McCombie 1989; Kuensel 2010b). For instance, recently, the death of a suspected rabid cow in one of the villages in southern Bhutan caused panic among the people after milk from the cow was consumed, but it was not laboratory examined and confirmed due to logistic reason. This resulted in increased demand for post exposure anti-rabies vaccination of more than 200 people (Kuensel 2010b). Similar incidents have occurred in Bhutan during previous outbreaks, requiring mass post exposure vaccination of people (normally category I exposure) (Kuensel 2009b; Tenzin et al., 2010a; Tenzin et al., 2010b). Therefore, following WHO recommendations, based on the category of exposure and the epidemiological likelihood of the implicated animal being rabid to make a decision about PEP would avoid unnecessary PEP and reduce the expenditure (WHO, 2010a).

Furthermore, our study also shows that 43 people were given rabies PEP following rat bites (Table 9.1). Rat rabies is a rare phenomenon and may represent only incidental infection of rats by dog or cat attacks or by eating infected dog or cat carrion (Sriaroon et al., 2005; Kamoltham et al., 2002). House rats and mice (and rodent species in general) are not a natural reservoir of rabies and post exposure prophylaxis is seldom indicated for rat bites (Sriaroon et al., 2005; Corey and Hattwick 1975). In addition, several field studies in other countries have not recovered rabies virus from sampled rats (Sriaroon et al., 2005; Kantakamalakul et al., 2003; Patabendige et al., 2003; Wincewicz 2002).

Unlike other vaccines, PEP for rabies requires repeated visits by the patient to the hospital to complete a full course within 28 days (e.g. Essen regimen). Therefore, patient compliance is important for adequate immunization (Madhusudhana et al., 2002). Our analysis shows that about 40% of patients received an incomplete vaccine course (<5-dose course) between 2005 and 2008. Analysis of the dataset shows that patients presenting to hospitals in rabies risk areas (rabies outbreak or endemic area) were less likely to have an incomplete course of the vaccine. Among the incomplete recipients of vaccine, almost half of the patients were from the interior of Bhutan where the risk of infection – even if they were left untreated – was low or non-existent since there have been no reported rabies cases in dogs in the interior of Bhutan for at least 18 years (Tenzin et al., 2010a). Similarly, animal bite victims are less likely to have an incomplete course than non-bite exposures (which pose less risk of infection). One study in Thailand (Sriaroon et al., 2005) have shown that almost one-third of the dog bite patients neglected to come for the last dose (day 90) of the vaccine series (Thai Red Cross ID regimen) and did not complete a full vaccine series. Asian Rabies Expert Bureau (AREB) members emphasized the need for a simplified PEP protocols-requiring reduced number of clinic visits (Dodet, 2010). The shortening of time to complete the PEP vaccination schedule would help in increasing the patient compliance for completion of the PEP course and also would reduce the burden on patients, in terms of loss of time for work and transportation cost (Dodet, 2010; Shantavasinkul et al., 2010). However, research is ongoing to develop shorter schedules of PEP regimen. For example, most recently, a reduced dose rate – 1ml dose each on day 0, 3, 7, 14 (4 intramuscular injection) that complete the course within two weeks was introduced and recommended by US-CDC (Rupprecht et al., 2009; Rupprecht et al., 2010), and even shorter schedule “one week, 4-site” (4-site intradermal injections on day 0, 3 and 7), developed by the Thai Red Cross and the Queen Saovabha Memorial Hospital in Bangkok, Thailand (based on their preliminary findings) have shown a significantly ($P < 0.001$) higher geometric mean titer of rabies neutralizing antibodies on days 14 and 28 than the WHO approved Thai Red Cross (TRC) ID regimen (2-site ID injections on each days 0, 3, 7, and 28) (Shantavasinkul et al., 2010; Warrell et al., 2008) .

Post exposure treatments are provided free of charge, resulting in substantial cost to the primary health care system in Bhutan. For instance, the government spent about Bhutanese ngultrum (Nu.) one million for rabies vaccine from 2002 to 2005 and the expenditure increased to Nu.5.878 million in 2006 (Nu.45 = 1 US$) (Kuensel 2007). Similarly, it has been estimated that post exposure treatment (rabies vaccine) in humans accounted for most of the cost during the time of rabies outbreak in Bhutan (Tenzin et al., 2010b). Although WHO guide lines do not recommend PEP for category I exposure (WHO, 2010a), PEP is still being provided in Bhutan for these categories of exposures. If rabies vaccine injection is at all necessary and demanded by the people (BBS, 2010; McCombie 1989) (in situations such as ingestion of cooked meat and dairy products derived from a rabies suspected or confirmed animal), we recommend that intra-dermal regimens be considered for these category of exposure and can reduce the cost of treatment by about 70%, compared to conventional intramuscular regimens (Khawplod et al., 2006; Wilde et al., 1999). The intra-dermal regimes have been successfully used in many rabies endemic countries in Asia – including Thailand, Sri Lanka, The Philippines, and India – and have been found to be equally immunogenic and as effective as that of the standard intramuscular regimen (WHO, 1996; Madhusudhana et al., 2002; Khawplod et al., 2006; Wilde et al., 1999; Brown et al., 2008; Brown et al., 2011).

Finally, the overall goal of public health policy should be to reduce post exposure treatment in humans by conducting proper risk assessment, public awareness education programs and by increasing vaccination coverage in dogs (WHO, 2010a). Mass vaccination of dogs have been documented to be a more beneficial, less expensive, logical and ethical way to control rabies in animals than mass post exposure treatment of people alone in resource-limited countries (Bodel and Meslin 1990; Zinsstag et al., 2007; Kayali et al., 2006). A One-Health approach should be encouraged and strengthened by collaboration and pooling of resources between public health and veterinary services for rabies control program in Bhutan. Sharing of information about the local epidemiology of rabies in animals between animal and human professionals can help the clinician to make appropriate decisions for post exposure treatment in Bhutan. A thorough assessment of each individual case by following the WHO guidelines and decision making pathway algorithm (a flow-chart with a decision-making tree) (Corey and Hattwick 1975; Moran et al., 2000; Rupprecht and Gibbons 2004; Dubnov et al., 2006; WHO, 2010a; Dodet, 2010) would reduce the overuse or misuse of the post exposure treatment, and therefore reduce expenditure in Bhutan. We also recommend improving the country-wide PEP rabies surveillance system in hospitals and Basic Health Units by updating the database management and reporting system. This would provide a means to assess the expenditure and status of the rabies control program.

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