Rabies Postexposure Prophylaxis Noncompletion After Dog Bites: Estimating the Unseen to Meet the Needs of the Underserved

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Conflict of Interest

Dr. Philippe Buchy is currently an employee of GSK Vaccines

Running head: IDENTIFYING RABIES VACCINE-UNDERSERVED AREAS

List of abbreviations

PEP: post-exposure prophylaxis

IPC: Institut Pasteur du Cambodge

RI: Rabies Index

CI: Confidence interval

WHO: World Health Organization

OR: Odds-ratio

RR: Relative risk

ARP: Attributable risk percent

SD: Standard deviation

IQR: Interquartile range

rpc@ipc: Rabies Prevention Center at the Institut Pasteur du Cambodge

AUC: Area under the receiver operating curve

BRT: Boosted regression tree

Abstract:

Post exposure prophylaxis prevents human rabies and is accessible in Cambodia principally in Phnom Penh, the capital. Timely, affordable access to post-exposure prophylaxis is a challenge for the mainly rural population. We aimed to identify districts independently associated with post-exposure prophylaxis (PEP) noncompletion to position frontline vaccination centers. We analyzed the 2009-2013 database at the rabies prevention center of the Institut Pasteur du Cambodge, Phnom Penh. Logistic regressions identified non-geographic determinants of PEP noncompletion and districts after adjustment for these determinants. The influence of distance by road was estimated using a boosted regression trees model. A district noncompletion population attributable fraction (Rabies Index) was computed and mapped. A cartographic analysis based on the statistic developed by Getis and Ord identified clusters of high-Rabies Index districts. Factors independently associated with noncompletion were patients' district of residence, male gender, age 15 to 49, initial visit during rice harvest, the dog's status (culled or disappeared) as well as a prescribed PEP protocol requiring more than three PEP sessions (four and five). Four clusters of high-Rabies Index (RI) districts were identified using this analytical strategy applicable to many vaccination or other health services. Positioning frontline PEP centers in these districts will significantly widen access to timely and adequate PEP.

Key words: rabies; post-exposure prophylaxis; vaccine; dogs; epidemiology; access; observance; Medically Underserved Area

Introduction

Human rabies after an animal bite is prevented by immediate wound cleansing and antisepsis followed by timely and adequate postexposure prophylaxis (1). Pioneered by Louis Pasteur in 1885(2), postexposure prophylaxis entails the intramuscular or intradermal administration of rabies vaccine, with or without rabies immunoglobulin (1). Although rabies postexposure prophylaxis is available in Cambodia, most Cambodians face daunting obstacles to access and observe timely, adequate and affordable postexposure prophylaxis in the rural setting (3). A model-based estimate of rabies deaths in Cambodia concluded to 810 human rabies deaths in 2007 (95%CI: 394-1,607), for an estimated incidence of 5.8/100,000 (95% CI: 2.8-11.5), the highest published worldwide (4). As efforts are renewed to control dog-mediated rabies (5), we sought to identify factors associated with postexposure prophylaxis (PEP) noncompletion in the Rabies Prevention Center at Institut Pasteur du Cambodge database (Institut Pasteur du Cambodge, Phnom Penh) to optimally position frontline centers and improve geographical access to PEP for underserved Cambodians.

Methods

Since 1998, Rabies Prevention Center at Institut Pasteur du Cambodge staff prospectively enter data on patients and dogs for every initial and follow-up patient visits using a standardized questionnaire (> 21,000 referrals each year). Some patients bring the biting animal's severed head to Institut Pasteur du Cambodge for testing at the National Reference Center for rabies (Virology Unit, Institut Pasteur du Cambodge). Brain samples are screened by direct fluorescent test using a fluorescent lyophilized, absorbed anti-rabies nucleocapsid conjugate (Bio-Rad, Marnes-la-Coquette, France) (6). We extracted an anonymized version of the Rabies Prevention Center at Institut Pasteur du Cambodge database. Factors studied included gender, age, province/district of residence and the date of referral. Exposure characteristics included time lapse before referral, type of exposure, anatomical site of main wound and World Health Organization (WHO) exposure category (1). Further characteristics included whether the attack was provoked, the animal's behavior, status at patient referral and ownership and laboratory results if the animal's head was brought to Institut Pasteur du Cambodge for testing. The Rabies Prevention Center at Institut Pasteur du Cambodge staff administers World Health Organization-recommended PEP protocols (1). Prior to 06/06/2012, the recommended PEP was based on a Thai Red Cross intradermal protocol of five sessions (two intradermal doses at Days 0, 3, 7 and one intradermal dose at Days 28 and 90) if the animal died, was put down, was lost or tested rabies-positive. After 06/06/2012 the full protocol was shortened to four sessions of two intradermal vaccine doses (1). The protocol was considered non-observed/noncompleted if terminated by the patient before the fifth ("full PEP" before 06/06/2012) or the fourth session (beginning 06/06/2012), unless: 1/ the animal was alive at Day 10 (stop after the third session); 2/ the patient had been previously immunized as per vaccination records (stop after the second, booster session); 3/ or if the dog's head tested negative (discontinue after the first session).

We interviewed the Head of each of Cambodia's 159 district health centers by phone. We documented the distance by road in kilometers, travel time (minutes) and estimated cost (in Riels; 1 US$ = 4,000 Riels) from the district center to Phnom Penh, as well as the months of flooding and rice harvest. Stung Treng, Mondulkiri, Ratanakiri, Otdar Meanchey, Pailin and Kep provinces were excluded as their districts contributed less than five patients, a number too low to be further analyzed.

Determinants were described and compared between rabies PEP completers and noncompleters (Wilcoxon test for quantitative variables and Chi-square for percentages, Chi-square for trend for years). Patients' age was categorized into three classes (<15 years; 15-49; >50) and date of referral into a binary variable (during/after the time at which 75% of districts have harvested rice paddy fields). Variables explored for association with noncompletion were year and time of year of referral, time lapse between bite and patient referral, sociodemographic variables (age, gender), characteristics of the exposure (type, severity and anatomical site of the exposure), characteristics of the dog (behavior, ownership, rabies confirmation status) and of PEP sessions. Variables associated with noncompletion in univariate analysis with a significance level of $p<0.2$ were all included in a multivariate logistic regression model. Factors independently associated with a p value <0.05 were retained in the model through a backward selection, using Wald's test. A second logistic regression model was developed in the same way, this time to quantify the association of district of residence with PEP noncompletion, adjusted for all non-geographical factors independently associated with noncompletion in the previous multivariate model. The models' discriminating power was evaluated by computing the area under the receiver operating characteristic curve.The relationship between the distance to the PEP center (measured as Euclidian, distance by road, travel time or travel cost to Doun Penh district where Institut Pasteur du Cambodge is located) and the probability of four-session ("full")-PEP noncompletion was suspected to be nonlinear. Boosted Regression Trees models fitting complex nonlinear relationships (7) were therefore used to assess independently the role of each distance measurement variable adjusted for non-geographical variables (7). The model with the highest area under the receiver operating curve (using distance by road) was retained and provided a full-PEP noncompletion cutoff for distance to Rabies Prevention Center at Institut Pasteur du Cambodge.

The risk of noncompletion in a district was quantified by computing an attributable risk percent in those exposed (8). This percentage estimates the proportion of people who refer but do not complete PEP after a bite by a potentially rabid dog. It is computed using a relative risk (8). The models used, however, compute an Odds-ratio of non-completion. The Odds-ratio was deemed to approximate the relative risk well because the probability of noncompletion was low (<10%) (9,10). The ensuing Rabies Index is an absolute number, computed by multiplying the attributable risk percent exposed by the estimated number of dog bite victims, itself a product of the population of the district (11) and the annual dog bites incidence documented by another, prospective Institut Pasteur du Cambodge study (12).The Rabies Index is therefore a measure of impact which reflects the theoretical PEP noncompleter caseload in a given district that is underserved by the current centralized rabies prevention center and which in theory would better access and complete timely and adequate PEP if it were made available in or close to that district:

$$RI_{district\ (i)} = ARP_{ex} * N_{bitten} = ((RR - 1) / RR) * (incid_{bites} * pop_{district})$$

Where ARP_{ex} = attributable risk percent exposed; N_{bitten} = number of dog bite victims expected annually in the district; RR = relative risk; $incid_{bites}$ = annual incidence of dog bites extrapolated to district(12) *; $pop_{district}$ = 2008 population of the district* (11).

The Rabies Index therefore estimates the number of noncompleted PEP which could theoretically be avoided in a district if all victims seek PEP and a center is located in that district.

Finally, we mapped the Rabies Index for all districts in Cambodia. A Rabies Index value of 0 was attributed to Phnom Penh, districts located within the noncompletion distance cutoff and districts not included in the analysis due to low representation in the database. We modeled the spatial relationship between districts using the Polygon Contiguity conceptualization method (13). A cartographic “hotspot” analysis of polygons representing districts was conducted based on the Getis-Ord Gi* statistic to assess spatial clustering of the Rabies Inidex (RI) indicator (14). Clusters of high-RI districts surrounded on all sides by other high-RI districts were considered significant hotspots when their Gi* p-value was <0.05 (z-score >1.96).

During the period covered, Rabies Prevention Center at Institut Pasteur du Cambodge data was entered using EpiInfo (Centers for Disease Control and Prevention, Atlanta, GA., USA). Statistical results were obtained using Stata 13 (Stata Corp., College station, TX. USA), R-3.1.0 (The R Foundation for Statistical Computing, Vienna, Austria). Spatial data and statistics were mapped using ArcMap 10.0 (Environmental Systems Resource Institute, Redlands, CA. USA).

This study received approval from the Cambodian National Ethics Committee for Human Research.

Results

The number of patients documented in the 2009-2013 (incl.) Rabies Prevention Center at Institut Pasteur du Cambodge (rpc@ipc) database as well as the data flow are shown in Figure 1.

The descriptive study bore on a total of 100,660 patients exposed to potentially rabid dogs who referred to Institut Pasteur du Cambodge (IPC) for PEP after a Category II or III exposure (Table 1). Patients were male in 52.4% of cases and their mean ± SD age was 21.2 ± 18.7 years (median 13; IQR 6 - 32), residing in 18 of Cambodia's then 24 provinces. Overall, 92,104 (91.5%) patients resided in five provinces located in or around the capital, Phnom Penh, which itself contributed 44,573 (42.3%) patients. The mean ± SD delay between exposure and first injection was 1.64 ± 2.01 days with a median of 1 day (IQR 1 – 2). The exposures all required PEP, among which 74,382 (74.0%) were Category II and 26,068 (26.0%) were Category III exposures. The dog's owner was identified in 99,648 (99.0%) cases and the dog appeared ill in 2,163 (2.1%) cases. Exposures occurred to lower extremities in 65,323 (64.9%) cases and to the head and neck in 6,178 (6.1%) cases. During the study period, 1,864 biting dog's heads were brought to the center and analyzed at IPC's virology unit, confirming rabies in 1,098 (58.9%) dogs. Prescribed PEP was considered non-completed in 7,814 (7.8%) of all cases, including 7,618 (7.6%) bites (Table 1).

The year (chi-square for trend $p<0.001$) was significantly associated to PEP noncompletion, as was the number of prescribed PEP sessions ($p <0.001$) (Table 1): 1,030 (25.0%) of intended 4-session PEP and 4,744 (58.4%) of intended five-session regimens (the rpc@ipc reference protocol to June 2012) were not completed. Compared to completers, PEP noncompleters tended to refer later after a bite and to be more frequent among male patients.

There was no statistically significant difference between PEP completers and noncompleters in terms of WHO bite category. Among PEP noncompleters, the dog's owner was less often identified and the dog had more often died, been put down or lost to follow-up. Finally, the proportion of patients who brought a head for testing was higher among PEP noncompleters.

PEP noncompletion was significantly higher during rice harvest, rising to 8.7% in November-April compared to 7.1% the rest of the year ($p<0.001$). The rainy season (and floods) was not associated with noncompletion. Noncompleters traveled significantly greater distances, had longer transportation times and higher transportation costs compared to PEP completers (Table 1).

Factors independently associated to PEP noncompletion were year, time lapse before PEP, age 15-49, referral during the rice harvest, the fact that the dog had been put down or lost to follow-up, and a prescribed regimen requiring more than three sessions (four and five sessions) (Table 2). Factors independently associated with PEP completion were being of female gender, , the biting dog appearing sick and laboratory-confirmed rabies in the biting dog's head.

The district of residence was significantly associated to PEP completion after adjustment for the non-geographic characteristics mentioned above. Among Cambodia's 132 districts, 24 (18.2%) were associated with a significant odds ratio of noncompletion, the highest being Tbaeng Meanchey district, Preah Vihear province (Table 3). Districts with statistically significant odds ratios (OR) for PEP noncompletion were generally the most distant from IPC and with lower population densities. The AUC analysis showed that the multivariate model had very good discrimination (88.0%).

Distance by road, travel time and travel costs were highly correlated. The model found to have the highest AUC was based on distance by road in kilometers; This variable was thus maintained in the BRT model. The representation of noncompletion dependence with distance by road after adjustment for non-geographic factors confirmed nonlinearity and estimated a cutoff of approximately 150 km beyond which the noncompletion percentage increased significantly for intention-to-treat by full four- or five-session protocols (Web figure 1).

Web figure 2 presents a map of districts by RI as well as borders for clusters of underserved, high-RI districts (Gi* z-scores > 1.96). This cluster analysis identified two large clusters of underserved districts: At least one frontline rabies prevention center can thus be optimally positioned in Bat Dambang (Battambang) and Prey Veng provinces to serve these districts as a public health priority while other districts closer to Phnom Penh can benefit from information before frontline centers can be opened secondarily (Web figure 2).

Discussion

Canine-mediated rabies is ~100% fatal but timely and adequate PEP is ~100% effective. Long-term rabies control and elimination can only be obtained by immunizing dogs (15). There is, however, a lag time between the initiation of dog vaccination programs and consequent reduction in human rabies deaths (16,17). During that time, lives can be spared by timely, adequate and affordable PEP - a very highly effective intervention, especially in rabies-endemic settings (18,19). This is a considerable challenge, especially in the rural areas of endemic developing countries where most rabies cases occur. In 2008, 80.5% of the Cambodian population (67% of which lived in 10 southeastern provinces) was rural (11).

Few studies have been carried out on the determinants of PEP noncompletion.(20) Our global percentage of noncompleters (7.8%) is lower than that reported at Queen Saovabha Memorial Institute in Bangkok, Thailand (22.6%) but remains high in Cambodia where canine rabies is widespread and highly enzootic (20). The rabies burden in dogs was reduced in Thailand, perhaps reducing perceived risk and completion (22). In several IPC studies, rural Cambodians were keenly aware of the transmission mode and lethality of rabies (21). Lastly, rabies PEP is subsidized at IPC but not cost-free. This may incite patients to return and complete a PEP protocol for which they have entirely paid for up front.

Our study enabled us to better identify factors independently associated with rabies PEP noncompletion in Cambodia: Male patients aged 15-49 andthose exposed to a dog put down or lost to follow-up were more likely to discontinue the PEP regimen, likely because they resided in distant rural villages. Noncompletion was especially frequent during rice harvest - when rural Cambodians face the stark choice of ensuring livelihoods for the year or spend precious money and time to return to Phnom Penh and continue PEP. Such assessments may need to be repeated regularly, as shown by the significant association with year studied, changes in epidemiology and road network and use. Some districts close to Phnom Penh were also independently associated with noncompletion, but not because of distance: These areas will likely benefit from reinforced messages rather than from positioning another center nearby.

Beyond a certain distance, however, information alone will not reduce noncompletion. Making PEP accessible throughout Thailand greatly reduced reported human rabies cases (17,23). Our study identified districts where rabies PEP outposts can be positioned with the greatest benefit for Cambodians: Distance was identified as an independent noncompletion factor for full PEP protocols, with a cutoff estimated at 150 km by road. Furthermore, the number of patients residing in various Cambodian districts expected to discontinue protocols early (assuming a generalizable incidence of bites and applying it to population figures) gave an indication of underserved areas.

Allocating scarce resources to a large number of people at medium risk of a disease not transmissible from person to person is more effective than allocating them to a small number of people at high risk (24). The choice was made to position rabies prevention centers in areas with the highest anticipated impact. To do so, we computed a composite index, postulating that: 1/ the Odds-ratio for noncompletion was a good approximation of the Relative Risk, which is considered the case when the event is infrequent (<10%) (9,10); 2/ The number of expected PEP regimens resulted from the population size and the incidence of dog bites, the latter extrapolated to all Cambodian districts; 3/ The 2008 population census data was a good approximation of the population and its distribution across districts for the study period. Our original strategy can be used in complement to seroepidemiological studies and registries to identify underserved areas and quantify needs (25,26).

Our study may have biases and limitations. One, extrapolating one district's dog bites incidence rate to all districts in Cambodia may misestimate the true rate. This, however, is the best available estimate and 80% of the Cambodian population lives in similar villages. Two, roads progressively improve in Cambodia: Difficulty to reach IPC may change over time. Conversely, road traffic, travel times and prices continue to increase. We accounted for this by examining only data from recent years. Three, our models did not adjust for patients' socio-economic status, which is not routinely collected at IPC. Distance, rural living and being affected by the rice harvest, however, are good proxies for low socio-economic status, which does not differ greatly across populations in rural Cambodia (in 2008, the third-quartile monthly disposable incomes *per capita* in rural Cambodian households was around US$ 40.00 (27)). Four, the database cannot differentiate between patients bitten by "observable" dogs at baseline which were alive after ten days (no need to return for a fourth session) and patients bitten by dogs that died during the first week who should have returned for a fourth session; Among the 87,558 patients bitten by an observable dog at baseline, 2,064 (2.3%) were noncompleters. In absence of dog veterinary quarantine services, this shortcoming cannot be addressed. Five, errors may occur during data entry in a busy rabies prevention center. This may have occurred, but random entry errors are unlikely to have affected results due to the large number of patients included in this analysis. Systematic errors which may have occurred due to variables being documented by the same team throughout the study period are unlikely linked to PEP being completed by the patient. Finally, our strategy is based on examining noncompletion in people who referred to rpc@ipc, but cannot account for people who did not, especially from Western Cambodia. Although this is unavoidable, our strategy covers most Cambodian districts (home to 95.4% of the entire Cambodian population, including Phnom Penh) and compensates by mapping districts' *expected* number of PEP noncompleters.

As in the seminal work by A. Wald on damaged yet surviving planes (28), attempting to measure what we do not see rather than what we see is challenging. Aside for a very recent study (29), previous published attempts to map underserved areas or populations are overwhelmingly based on estimates of distance and travel times (30–32). Using a real-world database to map underserved district *clusters* based on the Gi* Getis statistic (14) enabled us to identify neighboring areas with a high Rabies Index, thereby reflecting a more reliable estimate of the high number of anticipated noncompleters and improving cost-effectiveness. This innovative strategy can be applied to any public health measure, including screening or care services, as long as: 1/ The risk of disease is known or can be extrapolated throughout the country; 2/ the risk is below 10%, 3/ District populations are reasonably well documented; 4/ The patient databases analyzed are near-exhaustive for most of the territory being examined. It can also be added to the toolkit for rabies elimination as WHO leads renewed efforts to eliminate dog-mediated, human rabies deaths (5,33).

Cambodian authorities have committed to eliminating canine rabies by 2030 (34). This ambitious task will take time, during which improving access to timely, affordable and adequate PEP would spare human lives in Cambodia. Institut Pasteur du Cambodge will assist in optimally positioning frontline sites to improve geographical access to PEP. Access can also be improved by reducing the duration and doses of PEP protocols to keep costs down. As a research agency of the Cambodian Ministry of Health, IPC is working to attain this objective at no additional risk to patients.

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Conflict of Interest

Dr. Philippe Buchy is currently an employee of GSK Vaccines.

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Table 1: Characteristics of post-exposure prophylaxis (PEP) patients referred or self-referred after exposure to a potentially rabid dog, Rabies Prevention Center at Institut Pasteur du Cambodge (rpc@ipc) database 2009-2013, Phnom Penh, Cambodia.

Characteristic	Total N=100,660		Non-completed protocols N=7,814			Completed protocols N=92,846			p value
	n	IQR	n	%	IQR	n	%	IQR	
Patient characteristics									
Year									<0.001 [a]
2009	21,068		1,461	6.9		19,607	93.1		
2010	21,064		1,473	7.0		19,591	93.0		
2011	19,340		1,351	7.0		17,989	93.0		
2012	19,491		1,653	8.5		17,838	91.5		
2013	19,697		1,876	9.5		17,821	90.5		
Time lapse (days)									<0.001 [a,b]
Median (IQR)	1.0	1.0 – 2.0	1.0		1.0 – 3.0	1		1.0 – 2.0	
≤ 1 day	62,591		3,985	6.3		58,606	93.6		
> 1 day and ≤ 2 days	17,779		1,508	8.5		16,271	91.5		
> 2 days	20,290		2,321	11.4		17,969	88.6		
Age (years)									<0.001 [b,c]
Median	13.0	6.0 – 32.0	15.0		7.0 – 33.0	13.0		6.0 – 32.0	
Missing data	22		2	9.1		20	90.9		
<15 years old	52,175		3,823	7.3		48,352	92.7		
15-49 years old	37,155		3,096	8.3		34,059	91.7		
>50 years old	11,308		893	7.9		10,415	92.1		
Gender									<0.001 [c]
Male	52,761		4,265	8.1		48,496	91.9		
Female	47,899		3,549	7.4		44,350	92.6		
Type of exposure									<0.001 [c]
Scratch or lick on nonintact skin	210		196	93.3		14	6.7		
Bite	100,450		7,618	7.6		92,832	92.4		
WHO Category									0.108 [c]
Category I	0		NA			NA			
Category II	74,590		5,850	7.8		68,740	92.2		
Category III	26,070		1,964	7.5		24,106	92.5		
Anatomical site of main exposures									
Head and neck	6,178		513	8.3		5,665	91.7		0.101 [c]
Torso	8,928		623	7.0		8,305	93.0		0.004 [c]
Upper limbs	21,185		2,024	9.6		19,161	90.4		<0.001 [c]
Lower limbs	65,323		4,757	7.3		60,566	92.7		<0.001 [c]
Genitals	247		14	5.7		233	94.3		0.218 [c]
Type of attack									<0.001 [c]
Provoked	29,656		2,111	7.1		27,545	92.9		
Unprovoked	71,004		5,703	8.0		65,301	92.0		
Biting dog's behavior									<0.001 [c]
Sick	2,163		674	31.6		1,489	68.8		
Healthy	98,497		7,140	7.2		91,357	92.8		
Ownership									<0.001 [c]
Owned dog	99,648		7,476	7.5		92,172	92.5		
No identified owner	1,012		338	33.4		674	66.6		
Dog's status									<0.001 [c]
Put down	10,666		4,559	42.7		6,107	57.3		
Died	812		313	38.5		499	61.4		
Lost	1,623		877	54.0		746	46.0		
Alive	87,558		2,064	2.4		85,494	97.6		
Missing data	1		1	0.0		0	0.0		
Number of recommended PEP sessions									<0.001 [a]
Missing data	9		7	77.8		2	22.2		
1 session	765		0	0.0		765	100.0		
2 sessions (boosters)	1,277		22	1.7		1,255	98.3		
3 sessions	86,368		2,016	2.3		84,352	97.7		
4 sessions	4,121		1,030	25.0		3,091	75.0		
5 sessions	8,120		4,744	58.4		3,376	41.6		
Result of rabies testing									<0.001 [c]
Negative	765		0	0.0		765	100.0		
Positive	1,098		248	22.6		850	77.4		
Not tested / inconclusive	98,797		7,566	7.7		91,231	92.3		
District characteristics									
Rice harvest season									<0.001 [c]
No	57,036		4,040	7.1		52,996	92.2		
Yes	43,624		3,774	8.6		39,850	91.3		
District distance to Daun Penh District, Phnom Penh: Median									
Missing	137		16	0.2		121	0.1		
Euclidian distance (Km)	19.0	5.6 – 48.0	36.0		14.4 – 64.4	16.0		5.6 – 46.1	<0.001 [b]
Road distance (Km) [d]	30.0	8.0 – 60.0	57.0		22 – 95	25.0		8 – 60	<0.001 [b]
Travel time (minutes) [d]	60.0	30.0 – 90.0	60.0		40.0 – 120.0	60.0		30.0 – 90.0	<0.001 [b]
Travel costs (Riels) [d]	10,000	7,000 – 15,000	10,000		7,000 – 15,0000	10,000		8,000 – 20,000	<0.001 [b]

a: Chi-square for trend ; b: Wilcoxon test to compare medians; c: Chi-square test; d: For 100,523 (99.9%) patients

Table 2: Unadjusted and adjusted odds-ratios (OR) of non-geographical factors associated with rabies post-exposure prophylaxis (PEP) noncompletion and 95% confidence intervals (95%CI) following logistic regression (excluding district of residence), Rabies Prevention Center at Institut Pasteur du Cambodge (rpc@ipc) database 2009-2013, Phnom Penh, Cambodia.

Variable	Unadjusted OR			Adjusted		
	OR	95% CI	P value [a]	OR	95% CI	P value [a]
Year						
2009	1.0 (ref)		<0.001	1.0 (ref)		<0.001
2010	1.0	0.93, 1.1		1.1	1.0, 1.3	
2011	1.0	0.9, 1.1		1.1	1.0, 1.2	
2012	1.2	1.2, 1.3		4.4	3.9, 5.0	
2013	1.4	1.3, 1.5		10.0	8.9, 11.3	
Time lapse						
≤1 day	1.0 (ref)		<0.001	1.0 (ref)		<0.001
>1day and ≤2 days	1.4	1.3, 1.4		1.1	1.0, 1.2	
>2 days	1.9	1.8, 2.0		1.1	1.1, 1.2	
Age						
<15 years old	1.0 (ref)		<0.001	1.0 (ref)		<0.001
15 to 49 years old	1.1	1.1, 1.2		1.2	1.1, 1.3	
> 50 years old	1.1	1.0, 1.2		1.1	1.0, 1.2	
Gender						
Male	1.0 (ref)		<0.001	1.0 (ref)		0.006
Female	0.9	0.9, 0.9		0.9	0.9, 1.0	
Rice harvest season						
No	1.0 (ref)		<0.001	1.0 (ref)		<0.001
Yes	1.2	1.2, 1.3		1.2	1.2, 1.3	
Type of exposure						
Bite	0.006	0.003, 0.01	<0.001	0.02	0.01, 0.05	<0.001
Scratch/lick on nonintact skin	96.6	63.7, 146.6	<0.001	1.13	0.20, 6.53	0.888
WHO Category						
Category II	1.0 (ref)		0.10	1.0 (ref)		0.290
Category III	1.0	0.9, 1.0		0.96	0.89, 1.03	
Anatomical site of exposure [b]						
Head and neck	1.1	1.0, 1.2	0.11	0.87	0.67, 1.12	0.282
Torso	0.9	0.8, 1.0	0.004	0.90	0.78, 1.04	0.156
Upper limb	1.3	1.3, 1.4	<0.001	0.99	0.91, 1.05	0.570
Lower limb	0.8	0.8, 0.9	<0.001	0.95	0.87, 1.04	0.297
Genitals	0.7	0.4, 1.2	0.211	NA	NA	
Type of attack						
Unprovoked	1.0 (ref)		<0.001	1.0 (ref)		0.047
Provoked	0.9	0.8, 0.9		0.9	0.9, 1.0	
Biting dog behavior						
Healthy	1.0 (ref)		<0.001	1.0 (ref)		<0.001
Sick	5.8	5.3, 6.4		0.49	0.4, 0.6	
Ownership						
Owned dog	1.0 (ref)		<0.001	1.0 (ref)		0.093
No identified owner	6.2	5.4, 7.0		0.86	0.72, 1.02	
Dog's status						
Put down	30.7	29.0, 32.6	<0.001	1.7	1.4, 2.1	<0.001
Died spontaneously	26.4	22.8, 30.6		1.3	1.0, 1.7	
Lost	44.7	40.2, 49.6		2.3	1.9, 2.9	
Alive	1.0 (ref)			1.0 (ref)		
Rabies virological result in dog head [c]						
Positive	3.5	3.04, 4.05	<0.001	0.47	0.38, 0.59	<0.001
Not tested / inconclusive	1.0 (ref)			1.0 (ref)		
N visits needed for PEP completion						
Two visits	0.7	0.5, 1.1	<0.001	0.4	0.3, 0.7	<0.001
Three visits	1.0 (ref)			1.0 (ref)		
Four visits	13.9	12.8, 15.1		4.1	3.4, 5.041	
Five visits	58.8	55.3, 62.6		99.5	79.9, 123.9	

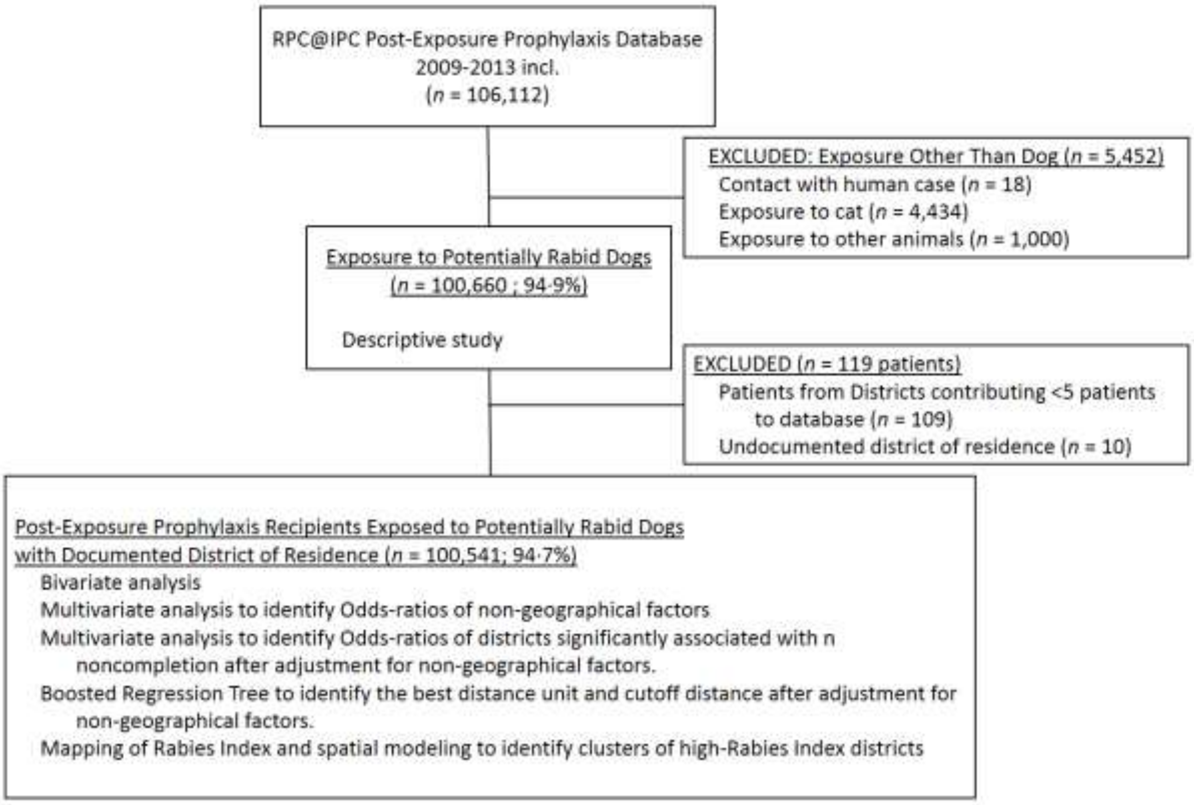
a: Likelihood ratio test; b: As patients were often injured at several anatomical sites, the reference class for each wounded anatomical site category is the absence of wound at that anatomical site; c: Heads tested negative and one-visit recommendations were removed from the model due to the absence of non-completion in these subjects; NA: not applicable as not included after unadjusted analysis due to p>0.2.

Table 3: Statistically significant Odds-ratio (OR) and 95% confidence intervals (95% CI) for PEP noncompletion by district of residence before and after adjustment for non-geographical factors, using Doun Penh district as reference, Rabies Prevention Center at Institut Pasteur du Cambodge (rpc@ipc) database 2009-2013, Phnom Penh, Cambodia.

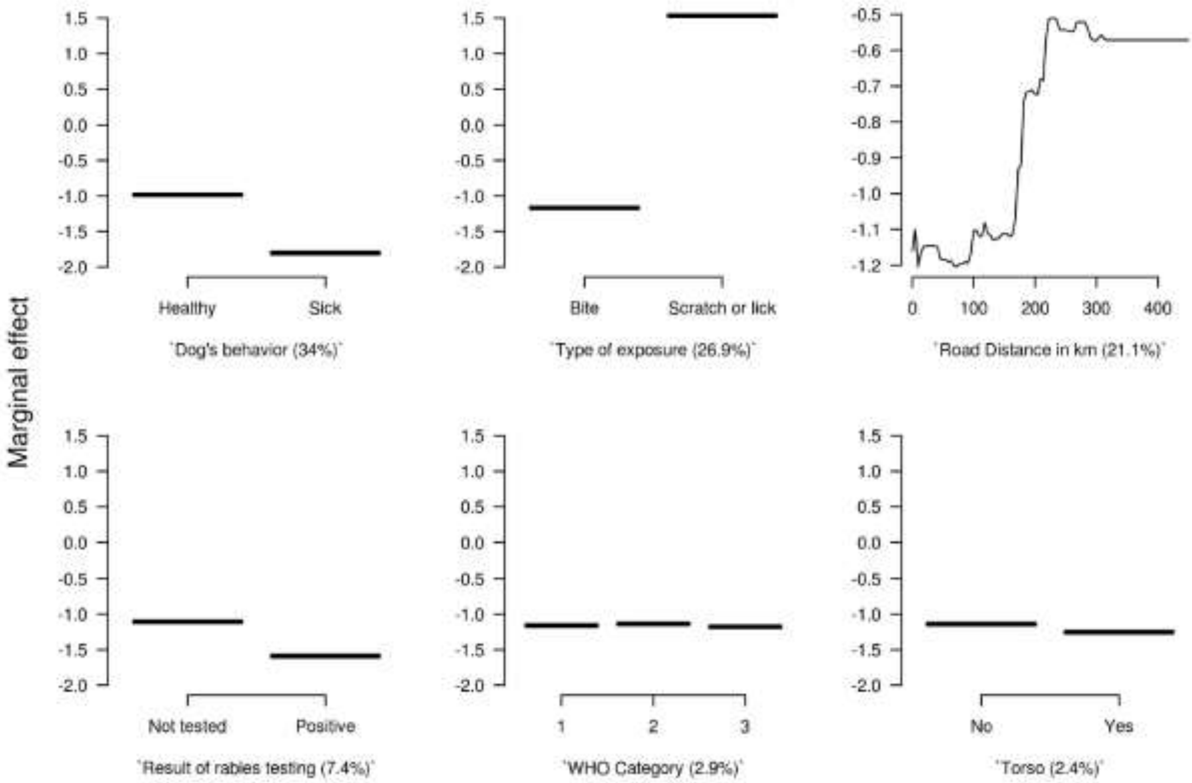
Province	Patients in database for Province	District [a]	Patients in database for District	Unadjusted			Adjusted		
				OR	95% CI	P value [b]	OR	95% CI	P value
IPC rabies center / Phnom Penh	38,875	Doun Penh	3,695	1.0 (ref)			1.0 (ref)		
Kandal	22,562	Khsach Kandal	4,346	2.89	1.06, 3.73	<0.001	1.36	1.06, 1.73	0.014
Kampong Cham	11,134	Memot	55	4.8	3.5, 6.8	0.1	0.30	0.09, 0.98	0.04
		Srey santhor	171	3.43	2.60, 4.54	<0.001	0.68	0.48, 0.97	0.03
Takeo	5,982	Kaoh Andet	12	1.22	0.29, 5.08	0.78	0.14	0.03, 0.75	0.02
Prey Veng	5,791	Me Sang	516	6.02	4.51, 8.02	<0.001	1.76	1.22, 2.53	0.002
		Kampong Trabaek	355	5.37	3.85, 7.51	<0.001	1.61	1.05, 2.46	0.03
Kampong Speu	4,110	Thpong	284	8.34	6.00, 11.58	<0.001	1.80	1.13, 2.854	0.01
Kampong Chhnang	2,358	Boribo	89	2.66	1.83, 3.86	<0.001	0.60	0.37, 0.95	0.03
Svay Rieng	851	Kampong Rou Reussey	92	4.62	2.51, 8.53	<0.01	2.44	1.12, 5.33	0.02
Battambang	285	Mong Reussey	42	6.61	3.00, 14.57	<0.01	4.30	1.39, 13.25	0.01
		Thmor Kol	18	8.03	2.61, 24.73	<0.01	5.26	1.38, 20.01	0.01
Pursat	247	Sampov Meas	56	6.87	3.47, 13.59	<0.01	3.80	1.45, 9.97	0.01
Banteay Meanchey	114	O Chrov	30	18.78	8.83, 39.71	<0.01	6.71	2.34, 19.22	<0.01
Preah Vihear	36	Tbaeng Meanchey	17	8.64	2.78, 26.88	<0.01	9.30	2.24, 38.55	0.002

a: Districts not appearing in this table are those associated with an OR found not significantly different from 1 after adjustment; b: Wald test.

Figure 1: Study data flow and analyses on patients referred or self-referred for post-exposure prophylaxis (PEP) after an exposure to a potentially rabid dog, Rabies Prevention Center at Institut Pasteur du Cambodge (rpc@ipc) database 2009-2013. Phnom Penh. Cambodia.



Web Figure 1: Boosted regression tree and partial dependences graphs showing influence >1% in probabilities after adjustment for other factors and 150-km distance from Phnom-Penh's Doun Penh District, the distance threshold for noncompletion of intended four-session post-exposure prophylaxis protocols, Rabies Prevention Center at Institut Pasteur du Cambodge (rpc@ipc) database 2009-2013. Phnom Penh. Cambodia.



Parameters used were as follows: a tree complexity (number of nodes) of 3, an initial number of trees set at 50, a learning rate of 0.001 and a bag fraction of 0.5. The y variable (outcome) was PEP noncompletion and the explanatory variables (x) were non-geographical factors which presented a p-value <0.2 in the initial univariate analysis mentioned above.

Web Figure 2: Underserved districts identified by (i) high odds-ratios (OR) of underrepresentation in the database and (ii) the Rabies Index (i), and 150-km distance (indicative) from Phnom-Penh's Doun Penh District, Rabies Prevention Center at Institut Pasteur du Cambodge (rpc@ipc) database 2009-2013. Phnom Penh. Cambodia.