Intradermal rabies post-exposure prophylaxis can be abridged with no measurable impact on clinical outcome in Cambodia, 2003–2014

Arnaud Tarantola, Sowath Ly, Malen Chan, Sotheary In, Yiksing Peng, Chanthy Chan, Chun Navy Taing, Chandara Chan, Sovann Ly, Simon Cauchemez, et al.

Vaccine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Intradermal rabies post-exposure prophylaxis can be abridged with no measurable impact on clinical outcome in Cambodia, 2003–2014

Arnaud Tarantola [a,b,*], Sowath Ly [a], Malen Chan [a], Sotheary In [a], Yiksing Peng [a], Chanthy Hing [a], Chun Navy Taing [a], Chandara Phoen [a], Sovann Ly [c], Simon Cauchemez [d], Philippe Buchy [e], Philippe Dussart [f], Hervé Bourhy [g], Jean-Yves Mary [h]

[a] Epidemiology & Public Health Unit, Institut Pasteur du Cambodge, Phnom Penh, Cambodia
[b] Epidemiology Unit, Institut Pasteur de Nouvelle-Calédonie, Nouméa, New Caledonia
[c] Center for Communicable Disease Control, Ministry of Health, Phnom Penh, Cambodia
[d] Mathematical Modelling of Infectious Diseases Unit, CNRS UMR2000: Génomique évolutive, modélisation et santé (GEMS), Center of Bioinformatics, Biostatistics and Integrative Biology, Institut Pasteur, Paris 75015, France
[e] GlaxoSmithKline, Vaccines R&D, Singapore
[f] Virology Unit, Institut Pasteur du Cambodge, Phnom Penh, Cambodia
[g] Institut Pasteur, Lyssavirus Dynamics and Host Adaptation Unit, WHO Collaborating Centre for Reference and Research on Rabies, Paris, France
[h] Inserm UMR 1153, Centre de Recherche Epidémiologie et Statistique Sorbonne Paris Cité, Hôpital Saint-Louis, Université Paris Diderot – Paris 7, Paris, France

ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Rabies
Post-exposure prophylaxis
Survival
Intradermal
Abridged regimens, Vaccine

ABSTRACT

Rabies causes 60,000 deaths worldwide annually. Rabies post-exposure prophylaxis is highly effective but often geographically and financially beyond reach in endemic developing countries. We conducted a retrospective study on clinical outcome at ≥6 months in 3318 Cambodians who received intradermal Vero cell vaccine post-exposure prophylaxis after a bite by a rabid or sick-looking but untested dog in 2003–2014. An external expert panel examined verbal autopsy reports to identify rabies deaths. 1739 (93.65%) persons bitten by rabid- and 1066 (72.96%) bitten by sick-looking but untested dogs were traced and 513 were lost to follow-up. Among the former, 1591 (91.49%) and 129 (7.42%) patients referred for 4+ and 3 post-exposure prophylaxis sessions, respectively. Three persons died of probable rabies so that the overall percentage of survival was 99.83% (95% exact confidence interval: 99.49–99.96%) in post-exposure prophylaxis recipients bitten by confirmed rabid dogs. No significant difference was found in survival among patients who received 3 *vs.* 4+ sessions (with or without rabies immunoglobin). The power of the study, however, was limited. The current four sessions/one month intradermal regimen can be reduced to a three sessions/one week at no detectable added risk to patients, with the limitation of study power at 49%. A clinical follow-up system should be adopted by rabies prevention centers, especially to monitor implementation of an abridged course. The Institut Pasteur in Cambodia regimen will improve vaccine equity by treating 33% more patients with available doses, reduce direct cost of vaccination, transportation and other indirect costs to vaccinees.

1. Introduction

Rabies is an infectious meningoencephalitis syndrome caused by rabies virus (RABV), the prototypical virus of the *Rhabdoviridae* family, *Lyssavirus* genus. Human rabies cases worldwide overwhelmingly follow a bite by a rabid dog [1]. After a bite, RABV transmission depends on various factors including bite severity and anatomical site and is inconstant. The outcome of clinical human rabies is almost always fatal, with only few known exceptions [2,3]. Rabies causes an estimated 60,000 cases worldwide every year and is emerging in previously unaffected areas of the World [1,4–6]. Rabies is almost 100% preventable by timely and adequate post-exposure prophylaxis (PEP).

Cambodia is a Southeast Asian country with a population of approximately 15 million, 75% of which reside in rural areas [7,8]. Dogs in Cambodia are overwhelmingly owner dogs. The incidence of human rabies in Cambodia, however, is among the highest worldwide due to a very high dog-to-human ratio and dog bite incidence as well as difficulties to access PEP [9–11].

* Corresponding author at: Epidemiology and Public Health Unit, Institut Pasteur du Cambodge, 5, Bvd. Monivong, BP 983 Phnom Penh, Cambodia.
E-mail address: arnaud.tarantola@pasteur.fr (A. Tarantola).

https://doi.org/10.1016/j.vaccine.2018.10.054
0264-410X/

The current dose-sparing, highly effective Thai Red Cross (TRC) PEP protocol entails four sessions of intradermal (ID) injection of two 0.1 mL vaccine doses over one month [12]. The cost of the protocol generates important issues, limiting access to PEP in the rural areas of developing countries where populations are most at risk of rabies [1,11,13]. An intradermal abridged protocol of three sessions over one week would reduce vaccine use per patient by 25%, allowing the treatment of 33% more patients with the same quantity of vaccine. It would improve equity and coverage, and reduce direct and indirect (travel...) costs to patients [14].

The objective of this RESIST (Rabies Elimination Support through Integrative Science and salvage Therapy) study was to document the clinical effectiveness of an intradermal abridged PEP protocol, comparing outcome in people who discontinued PEP after only three sessions *vs.* after the recommended four or more (4+) sessions of two 0.1 mL ID injections using Vero cell-based vaccine after a bite by confirmed rabid or by sick-looking but untested dogs, whether the latter were put down or escaped (henceforth referred to as "sick-looking or untested dogs").

2. Methods

2.1. Rabies center database

Clinical and epidemiological characteristics of patients referred each year for PEP at Institut Pasteur du Cambodge (IPC) are prospectively entered into a database since 1998. The same, trained team of clinicians and nurses systematically document patients. This team enters patients' self-declared village and district of residence, sociodemographic characteristics, dog and bite characteristics – including exposure category [12] – into an electronic form using EpiData (EpiData Association, Odense, Denmark) also used to monitor PEP sessions. An extraction of the database documents 203,519 Cambodian residents referred or self-referred to IPC after a dog bite over a period of 12 years, from January 1st, 2003 to December 31st, 2014, inclusive. Patients who were identified as previously vaccinated against rabies in IPC vaccination records or through the initial PEP interview were excluded from the analysis.

2.2. Virological testing at IPC

Heads of biting animals brought by about 2% of bite victims are also tested at IPC. After craniotomy and brain extraction, tissue samples are taken from Ammon's horn and the medulla oblongata [15]. As per WHO/OIE recommendations, samples undergo a direct fluorescent antibody test (DFAT) using an adsorbed, lyophilized anti-rabies nucleocapsid conjugate (#357-2112, Bio-Rad, Marnes-la-Coquette, France) according to the manufacturer's instructions [15]. Results are usually available on the day of the initial referral.

2.3. Rabies PEP at IPC

Since 2003, all rabies PEP for WHO Category II/III exposures [12] at IPC use Vero cell vaccine (Verorab®, Sanofi, France) administered to each deltoid intradermally (ID) using 25-gauge needles. In 2012, the full protocol changed from five to four sessions (Days 0, 3, 7 and 28) of two 0.1 mL ID doses as per WHO 2010 recommendations [12]. Due to chronic and severe shortages, available equine rabies immunoglobulin (ERIG) is administered in priority in case of positive DFAT results in the biting animal, sick-looking dogs or bites to the face, even in Category II exposures [11].

2.4. Callback at IPC

All previously unvaccinated patients bitten by rabid or sick but untested, non-surviving dogs who received ID Vero-cell based vaccine at IPC (with or without ERIG and whether or not they had returned for all prescribed PEP sessions of their own accord) between 2003 and 2014, inclusive, were eligible for the study. These were systematically traced back at least six months after initiation of PEP. Phnom Penh residents were excluded as initial attempts failed to identify any of these highly mobile persons. Since Cambodians cannot be reached by mail, the IPC team contacted the head of the health center nearest to the patient's village by phone to obtain the mobile phone number of the village chief. The latter was contacted to verify whether he knew of village resident of that name. If so, a telephone meeting was arranged with the person or kin, during which consent to participate was obtained (in Khmer). Patient identity and bite characteristics were verified without prompting. Outcome (patient dead, alive or lost to follow-up) was systematically entered in the database.

2.5. Verbal autopsy

If the patient was identified and traced back but had died, a verbal autopsy was conducted in Khmer by telephone with next of kin by an IPC doctor experienced in rabies using a standardized semi-structured interview form. All deaths were reviewed by an external panel of three rabies experts from India and Thailand on April 28th, 2017 to determine if they could be attributed to probable rabies as per established case definitions [16]. These experts were blind to the fatal cases' PEP status and our own conclusion.

2.6. Statistical analysis

Patients' baseline characteristics (sociodemographic, clinical and bite) and dog characteristics (including test results in dog heads when available), patients' PEP protocol completion and clinical outcome were assessed. Categorical variables were described as frequencies and percentages and continuous variables as median and interquartile range.

The overall percentage of rabies deaths among persons bitten by a rabies-confirmed dog or by a confirmed or sick-looking dog ("*any dog*") was computed, with exact 95% binomial confidence intervals (CI).

The proportions of rabies deaths by number of sessions were compared using unilateral Fisher's exact test and its mid-point p value to assess clinical inferiority of 3 sessions compared to 4+ sessions [17]. Rabies-attributed deaths that occurred before the date of the fourth session – termed "early deaths" – were not allocated *a priori* to a number of sessions and the various allocation hypotheses were explored. Denote N the number of early deaths. We computed the proportion π of patients in the 3-sessions group in our sample, after excluding the early deaths. We then derived, for $k = 0, \ldots, N$, the probability that k early deaths among N would have been allocated to the three-sessions PEP group if they had not died early. The sum of the Fisher mid-point p value for each value of k ($=0, \ldots, N$) weighted by their probability provided an overall Fisher p value taking into account the possible allocations of early deaths. This was done in patients bitten by confirmed rabid dogs and in patients bitten by "*any dog*".

After exclusion of the early deaths, the distribution of each baseline characteristic was compared between the 3 and 4+ sessions groups using Fisher's or Chi-square test for categorical variables and Wilcoxon test for continuous variables. Multiple logistic regression was used to assess the probability for a patient of belonging to the 3-sessions group according to patient's characteristics. The model was then used to compute for each early death

Please cite this article as: A. Tarantola, S. Ly, M. Chan et al., Intradermal rabies post-exposure prophylaxis can be abridged with no measurable impact on clinical outcome in Cambodia, 2003–2014, Vaccine, https://doi.org/10.1016/j.vaccine.2018.10.054

the probability to belong to the 3-sessions group and the overall Fisher p value was re-estimated.

Subsequent analyses were restricted to the most likely early deaths allocation hypothesis. The unconditional odds ratio was estimated through maximization of the likelihood and its mid-point-adjusted 95%CI was obtained by inverting the test [18]. Mid-point-adjusted power was estimated *post-hoc*, using an odds-ratio with a theoretical value close to that estimated.

Fisher's exact test and univariate regression were used to assess the association between each characteristic with rabies among patients bitten by confirmed rabid dogs. A multivariate logistic model was used to identify independent baseline characteristics associated with rabies and to assess the association with 3 *vs.* 4+ sessions, after adjustment for all these independently associated factors. A statistical significance threshold of 5.0% was used for all tests.

The Cambodian National Ethics Committee for Human Research approved the study.

3. Results

3.1. Patients

Between January 1st, 2003 and December 31st, 2014, inclusive, a total of 203,519 patients referred to IPC after a bite by a potentially rabid dog. In total, 3838 patients had not been previously vaccinated and were bitten by a confirmed rabid or sick-looking but untested dog, excluding surviving dogs (Fig. 1). Among these, 520 Phnom Penh residents were excluded from the analysis (Supplementary Table ST1). Among the 3318 patients living outside Phnom Penh included in the call-back procedure, 513 were lost to follow-up (Supplementary Table ST2): 118/1857 (6.35%) persons bitten by dogs with confirmed rabies and 395/1461 (27.04%) bitten by sick-looking but untested dogs, corresponding to a statistically significant difference in loss to follow-up ($p < 0.001$).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.10.054.

A total of 2805 previously unvaccinated patients living outside Phnom Penh who received ID PEP by Vero cell-based vaccine and with at least 6 months' follow-up were therefore included in the study (Table 1): 1739 (62.00%) were bitten by a dog with confirmed rabies and 1066 (38.00%) by an untested but sick-looking dog. In all, 2062 (73.54%) were contacted 12 months or more after PEP (median 31 months; IQR: 31.1–52.7; range 6–151).

3.2. Deaths

A total of 27 deaths were documented at least 6 months after PEP by verbal autopsy.

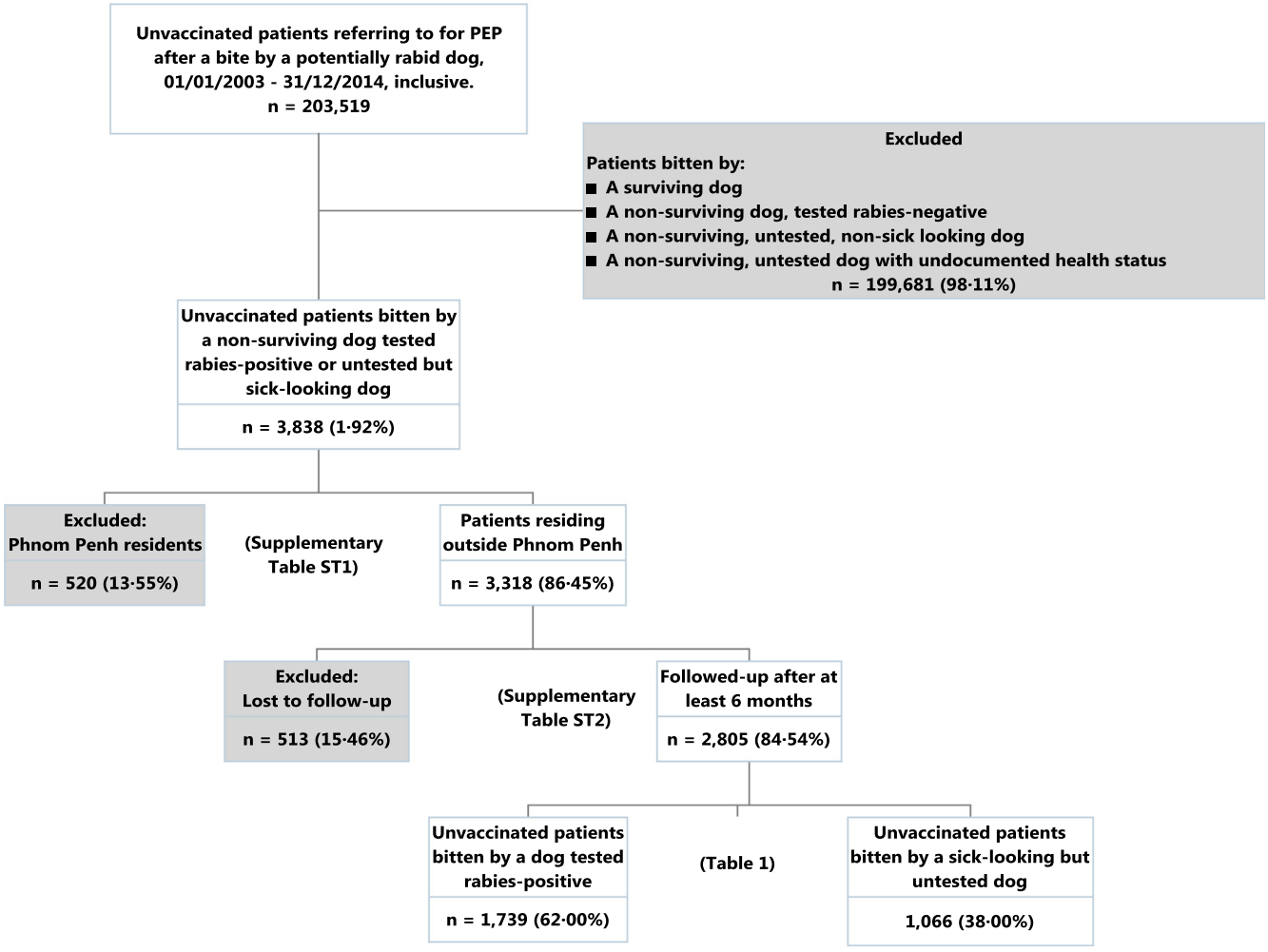

Fig. 1. Study data and patient flow, 2003–2014, Institut Pasteur du Cambodge. Legend: PEP – post-exposure rabies prophylaxis. Vaccination status was documented during the patient interview and by verifying in the IPC database. Dogs' sick appearance was documented based on patients' declaration only and entered into the database.

Please cite this article as: A. Tarantola, S. Ly, M. Chan et al., Intradermal rabies post-exposure prophylaxis can be abridged with no measurable impact on clinical outcome in Cambodia, 2003–2014, Vaccine, https://doi.org/10.1016/j.vaccine.2018.10.054

Table 1
Distribution of selected socio-demographic and baseline clinical characteristics of non-immune patients residing outside Phnom Penh, who received Vero cell-based rabies intradermal post-exposure prophylaxis after a bite by a confirmed rabid or a sick but untested dog (excluding surviving dogs) and not lost to follow-up, 2003–2014, Institut Pasteur du Cambodge.

	Patients bitten by		
	Rabies-confirmed dog (n = 1739)	Sick but untested dog (n = 1066)	«*Any dog*» (n = 2805)
Age (years) – median (IQR)	17 (9–37)	25 (12–45)	20 (10–40)
<15 years old	763 (43.88%)	349 (32.73%)	1112 (39.64%)
15–65 years old	915 (52.62%)	673 (63.13%)	1588 (56.61%)
>65 years old	61 (3.51%)	44 (4.13%)	105 (3.74%)
Male	999 (57.45%)	576 (54.03%)	1575 (56.15%)
Bite category [12]			
Category II	1218 (70.04%)	870 (81.61%)	2088 (74.44%)
Category III	521 (29.96%)	196 (18.39%)	717 (25.56%)
Anatomical site of the principal bite[*]			
Foot/leg	989 (56.90%)	624 (58.54%)	1613 (57.52%)
Hand	545 (31.36%)	335 (31.43%)	880 (31.38%)
Head/neck	136 (7.83%)	59 (5.53%)	195 (6.95%)
Other bite characteristics			
Number of bite wounds – median (IQR)	2 (2–2)	2 (2–2)	2 (2–2)
One bite wound	129 (7.42%)	121 (11.35%)	250 (8.91%)
Two bite wounds	1317 (75.73%)	834 (78.24%)	2151 (76.68%)
Three bite wounds or more	293 (16.85%)	111 (10.41%)	404 (14.40%)
Documented suture[◇]	14/376 (3.72%)	12/545 (2.20%)	26/921 (2.82%)
Clothes interposed	446 (25.65%)	261 (24.48%)	707 (25.20%)
Documented wound care[◇]	482/752 (64.10%)	235/652 (36.04%)	717/1404 (51.01%)
Dog status			
Spontaneous bite	1464 (84.19%)	815 (76.45%)	2279 (81.25%)
Sick-looking	1657 (95.28%)	1065 (99.91%)	2722 (97.04%)
Identified owner	1464 (84.19%)	879 (82.46%)	2343 (83.53%)
N persons bitten – median (IQR)	2 (1–3)	1 (1–2)	1 (1–3)
One person only	848 (48.76%)	621 (58.26%)	1469 (52.37%)
Two persons	417 (23.98%)	179 (16.79%)	596 (21.25%)
More than two persons	474 (27.25%)	266 (24.95%)	740 (26.38%)
Spontaneous death documented[°]	128 (7.36%)	115 (10.79%)	243 (8.66%)
Rabies testing	All tested positive	None tested	–
PEP characteristics			
Year of PEP – median (IQR)	2010 (2008–2012)	2013 (2011–2014)	2011 (2008–2013)
Delay before PEP (days) – median (IQR)	1 (0–1)	2 (1–3)	1 (1–2)
Same day (Day 0)	493 (28.35%)	137 (12.85%)	630 (22.46%)
After 1–6 days	1232 (70.85%)	875 (82.08%)	2107 (75.12%)
After one week (>Day 6)	14 (0.80%)	54 (5.07%)	68 (2.42%)
ERIG received	1677 (96.43%)	886 (83.11%)	2563 (91.37%)
PEP sessions – median (IQR)	5 (4–5)	4 (4–4)	4 (4–5)
1–2 sessions	19 (1.09%)	34 (3.19%)	53 (1.89%)
3 sessions	129 (7.42%)	128 (12.01%)	257 (9.16%)
4 or 5 sessions	1591 (91.49%)	904 (84.80%)	2495 (88.95%)
Follow-up			
Delay until callback (months) – median (IQR)	24.25 (6.57–47.33)	30.4 (21.2–46.27)	26.93 (9.7–46.87)
≥12 months	1001 (57.59%)	1061 (99.53%)	2062 (73.54%)

Abbreviations: IQR: interquartile range; PEP: post-exposure prophylaxis; ERIG: Equine rabies immunoglobulin.
[*] Non-exclusive categories as multiple bites on various anatomical sites are possible.
[°] The majority of biting dogs were immediately put down, before they could die spontaneously.
[◇] These variables were poorly documented.

Twenty-four were due to accidents (road accidents, drowning…) or chronic illness (old age, chest pain, ascites, etc.), two occurring in the three months following PEP (one liver cancer and one respiratory failure during pregnancy; both had received RIG and 4+ sessions).

The three remaining deaths were attributed to rabies by the external expert panel (Table 2). Rabies Cases 1 and 2 were bitten on the same day in the same province by different confirmed rabid dogs in different districts. They were referred to IPC on the same day. In total, 144 and 195 other study patients bitten by dogs with confirmed rabies received the vaccine and ERIG lots used in Cases 1–2 and Case 3, respectively, and survived. Case 3′s extensive head wound was sutured before referral to IPC for PEP. Cases 1 and 3 died before the planned date of the 4th PEP session (early deaths).

The number of rabies deaths by number of PEP session, with or without RIG and by dog rabid status is detailed in Table 3. In this Cambodian setting, the overall percentage of rabies following ID PEP is therefore 3/1739 (0.17%; exact 95% CI: 0.03–0.50%) after a bite by a dog with confirmed rabies and 3/2805 (0.10%; exact 95% CI: 0.03–0.33%) after a bite by "*any dog*".

3.3. Assessing clinical inferiority of 3 sessions compared to 4+ sessions

The probability for patients receiving more than 2 sessions to have referred for 3 sessions only was 127/1591 (7.39%). The probability that the two early deaths would have both received 3 sessions (Hypothesis 1), that one or the other would have received 4+ sessions (Hypothesis 2) or that both would have received 4+

Please cite this article as: A. Tarantola, S. Ly, M. Chan et al., Intradermal rabies post-exposure prophylaxis can be abridged with no measurable impact on clinical outcome in Cambodia, 2003–2014, Vaccine, https://doi.org/10.1016/j.vaccine.2018.10.054

Table 2
Details of probable rabies deaths in intradermal post-exposure prophylaxis recipients, 2003–2014, Institut Pasteur du Cambodge.

Case	Case 1	Case 2	Case 3
Sex	M	M	M
Age at PEP (years)	37	5	9
Province	Kandal	Kandal	Kandal
Date of bite	17-jul.-2008*	17-jul.-2008*	07-apr-2011
Date of PEP	17-jul.-2008	17-jul.-2008	08-apr-2011
Date death	5-aug-2008	1-sept.-2008	27-apr-2011
Days survived	19	46	19
N sessions completed	3	3	3
ERIG	Yes	Yes	Yes
Dog head	Positive	Positive	Positive
Bite category [12]	Category III	Category III	Category III
Anatomical site	Fingers	Head	Head
Signs	Hypersalivation and contracture	Fever and convulsions	Fever, convulsions, hypersalivation
Expert opinion	Rabies death	Rabies death	Rabies death

* Two patients bitten by two different dogs in two different districts, but first initiated PEP on the same day at Institut Pasteur du Cambodge.

sessions (Hypothesis 3) were therefore 0.55%, 13.69% and 85.76%, respectively. The sum of the mid-p values for Hypotheses 1–3, each weighed by their likelihood, yielded an overall unilateral Fisher mid-point estimate of 0.0959 (non-significant) when comparing deaths among patients who received 3 or 4+ sessions after being bitten by a dog with confirmed rabies (Table 4). The overall mid-point p value was 0.1158 (non-significant) for those bitten by "*any dog*" (Supplementary Table ST3).

The distribution of baseline characteristics of patients who received 3 PEP sessions *vs.* those who received 4+ sessions are presented in Table 5 (Table ST4 for patients bitten by "*any dog*"). Based on these data, the individual probabilities derived from the logistic model for the two early deaths to be allocated to the 3-sessions group were 7.23% and 7.34%, respectively, leading to an overall weighed Fisher p value of 0.0961, very close to the initial estimate of 0.0959.

Subsequent analyses consider the most likely hypothesis of the two early deaths occurring in the 4+-sessions group. The unadjusted odds ratio of the association between rabies death and receiving three PEP sessions only was estimated at 6.30 [95% CI: 0.21–83.30] for patients bitten by a dog with confirmed rabies and the mid-point-adjusted power was estimated at 49% for a theoretical odds-ratio of 6.50.

Table 6 describes the association between rabies death and baseline characteristics of patients after a bite by a dog with confirmed rabies (Table ST5 for "*any dog*"). In univariate analysis, Category III bites and principal bites to the head/neck were associated with a higher risk of rabies. The odds-ratio for bite category could not be estimated since the three deaths all suffered Category III bites. Consequently, no multivariate logistic model of rabies death could be derived (no convergence), making adjustment on independent characteristics impossible.

4. Discussion

We describe three probable rabies deaths among 1739 Cambodians traced at least six months after receiving PEP following a bite by a dog with confirmed rabies or among 2805 bitten by "*any dog*", with a percentage of PEP recipients alive at 6 months of 99.83% (exact 95% CI: 99.49–99.96%) and 99.89% (exact 95% CI: 99.67–99.97%), respectively. We were unable to demonstrate a statistically significant decrease in survival among patients who received 3 sessions when compared to 4+ sessions (with or without RIG). Adopting a 3-sessions regimen would share rabies vaccine doses more equitably, reducing vaccine use in patients by 25% and

Table 3
Number of patients alive and of probable rabies deaths at least 6 months after a bite by a confirmed rabid or a suspect but untested dog, stratified by number of intradermal post-exposure prophylaxis sessions and equine rabies immunoglobulin received and biting dog status, 2003–2014, Institut Pasteur du Cambodge.

Probable rabies death	Confirmed 1 session only		Confirmed 2 sessions only		Confirmed 3 sessions only		Confirmed 4+ sessions only		Received 3 sessions but could be allocated to 3 or 4+ sessions*		Any number of sessions		Total
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	
Confirmed rabid dog													
ERIG	5	0	4	0	119	1	1546	0	0	2	1674	3	1677
No ERIG	8	0	2	0	7	0	45	0	0	0	62	0	62
Subtotal	13	0	6	0	126	1	1591	0	0	2	1736	3	1739
Sick but untested dog													
ERIG	10	0	10	0	82	0	784	0	0	0	886	0	886
No ERIG	8	0	6	0	46	0	120	0	0	0	180	0	180
Subtotal	18	0	16	0	128	0	904	0	0	0	1066	0	1066
«Any dog»													
ERIG	15	0	14	0	201	1	2330	0	0	2	2560	3	2563
No ERIG	16	0	8	0	53	0	165	0	0	0	242	0	242
Total	31	0	22	0	254	1	2495	0	0	2	2802	3	2805

Abbreviations: ERIG: Equine rabies immunoglobulin.
* Two rabies-attributed deaths that occurred before the patients could have received the 4th session or not (early deaths).

Please cite this article as: A. Tarantola, S. Ly, M. Chan et al., Intradermal rabies post-exposure prophylaxis can be abridged with no measurable impact on clinical outcome in Cambodia, 2003–2014, Vaccine, https://doi.org/10.1016/j.vaccine.2018.10.054

Table 4
Rabies deaths observed by intradermal post-exposure prophylaxis completion allocation hypotheses for the two early deaths, Fisher mid-point p value per hypothesis, probability of occurrence of each hypothesis, and weighed Fisher mid-point p value, among patients bitten by a confirmed rabid dog, 2003–2014, Institut Pasteur du Cambodge.

PEP completion hypothesis	Observed	Hypothesis 1 *Both early deaths would not have completed the full 4+ protocol*		Hypothesis 2 *One of the two early deaths would have completed the full 4+ protocol*		Hypothesis 3 *Both early deaths would have completed the full 4+ protocol*	
Number of sessions completed		3	4+	3	4+	3	4+
N rabies deaths	3	3	0	2	1	1	2
N survived	1717	126	1591	126	1591	126	1591
Total	1720	129	1591	128	1592	127	1593
Unilateral Fisher mid-point value		0.00020642		0.0080455		0.1105589	
Probability of occurrence of hypothesis°		0.0054646		0.1369171		0.8576183	
Weighed overall unilateral Fisher mid-point value for all 3 hypotheses		0.0959					

Note: The individual probabilities derived from the logistic regression model for the two "early deaths" to be allocated to the 3-sessions group were 7.23% and 7.34%, respectively, leading to an overall weighed Fisher p value of 0.0961, very near to the initial estimate of 0.0959.
° Among only those receiving 3 or 4+ sessions and omitting the two early rabies deaths to allocate.

Table 5
Distribution of selected socio-demographic and baseline clinical characteristics of non-immune patients residing outside Phnom Penh, who completed 3 sessions *vs.* 4+ sessions of Vero cell-based rabies intradermal post-exposure prophylaxis and not lost to follow-up, after a bite by a confirmed rabid dog only, 2003–2014, Institut Pasteur du Cambodge.

	Patients who received		
	3 intradermal PEP sessions only* (n = 127)	4 or 5 intradermal PEP sessions (n = 1591)	p value**
Age (years) – median (IQR)	19 (11–35)	17 (9–38)	0.544
<15 years old	52 (40.94%)	703 (44.18%)	0.720
15–65 years old	71 (55.90%)	826 (51.92%)	0.386
>65 years old	7 (5.51%)	141 (8.86%)	0.195
Male	75 (59.06%)	911 (57.26%)	0.694
Bite category [12]			
Category II	90 (70.87%)	1112 (69.89%)	0.818
Category III	37 (29.13%)	479 (30.11%)	
Anatomical site°			
Foot/leg	75 (59.06%)	901 (56.67%)	0.601
Hand	38 (29.92%)	501 (31.51%)	0.711
Head/neck	9 (7.09%)	125 (7.86%)	0.754
Other bite characteristics			
Number of bite wounds	2 (2–2)	2 (2–2)	0.749
One bite wound	13 (10.24%)	114 (7.17%)	0.203
Two bite wounds	91 (71.65%)	1210 (76.05%)	0.266
Three bite wounds or more	23 (18.11%)	267 (16.78%)	0.700
Documented suture	0/27 (0.00%)	13/345 (3.77%)	0.612◇
Clothes interposed	31 (24.41%)	409 (25.71%)	0.833
Documented wound care	35/52 (67.31%)	444/695 (63.88%)	0.548◇
Dog status			
Spontaneous bite	111 (87.40%)	1337 (84.04%)	0.375
Sick-looking	119 (93.70%)	1520 (95.54%)	0.374
Identified owner	117 (92.13%)	1327 (83.41%)	**0.008**
N persons bitten	2 (1–3)	2 (1–3)	0.864
One person only	59 (46.46%)	778 (48.90%)	0.596
Two persons	35 (27.56%)	375 (23.57%)	0.310
More than two persons	33 (25.98%)	438 (27.53%)	0.707
Spontaneous death documented▽	6 (4.72%)	121 (7.61%)	0.232
PEP characteristics			
Year of PEP– median (IQR)	2009 (2007–2012)	2010 (2008–2012)	0.273
Delay before PEP (days)	1 (0–2)	1 (0–1)	0.125
Same day (Day 0)	35 (27.56%)	454 (28.54%)	0.814
After 1–6 days	91 (70.54%)	1125 (70.71%)	0.968
After one week (>Day 6)	2 (1.57%)	12 (0.75%)	0.322
ERIG received	120 (94.49%)	1546 (97.17%)	0.090
Follow-up			
Delay until callback (months) – median (IQR)	27.8 (6.6–51.3)	23.8 (6.6–47.1)	0.210
≥12 months	78 (61.42%)	910 (57.23%)	0.359

Abbreviations: IQR: interquartile range; PEP: post-exposure prophylaxis; ERIG: Equine rabies immunoglobulin.
* Excluding 2 patients who died before they could have received the 4th session or not.
** Fisher, Chi-square or Wilcoxon p-value (p-values < 0.05 shown in bold).
° On-exclusive categories as multiple bites on various anatomical sites are possible.
◇ These variables were poorly documented.
▽ The majority of biting dogs were immediately put down, before they could die spontaneously.

Please cite this article as: A. Tarantola, S. Ly, M. Chan et al., Intradermal rabies post-exposure prophylaxis can be abridged with no measurable impact on clinical outcome in Cambodia, 2003–2014, Vaccine, https://doi.org/10.1016/j.vaccine.2018.10.054

Table 6
Description of the association between rabies death and selected socio-demographic and clinical characteristics of non-immune patients residing outside Phnom Penh who received more than 2 sessions of Vero cell-based rabies intradermal post-exposure prophylaxis and not lost to follow-up after a bite by a confirmed rabid dog only, 2003–2014, Institut Pasteur du Cambodge.

Variable	Category	Rabies death	N alive	% death	p Fisher	Unadjusted Odds-ratio		p*
						Estimate	95% CI	
Age	Continuous	–	–	–	–	0.97	0.90–1.05	0.507
Age (years)	<15	2	754	0.26%	0.636	NE		
	15–65	1	902	0.11%			–	–
	>65	0	61	0.0%				
	<15	2	754	0.26%	0.586	2.55	0.23–28.22	0.444
	≥15	1	963	0.10%		Ref		
Sex	Male	3	985	0.30%	0.266	NE	–	–
	Female	0	732	0.0%				
Type of bite								
Bite category [12]	Category II	0	1202	0.0%	0.027	NE	–	–
	Category III	3	515	0.58%				
Anatomical site of principal bite**	Bite to the Foot/leg	0	976	0.0%	0.081	NE	–	–
	No bite to Foot/leg	3	740	0.40%				
	Bite to the hand	1	539	0.18%	1.000	1.09	0.99–12.07	0.943
	No bite to the hand	2	1177	0.17%		Ref		
	Bite to head/neck	2	133	1.51%	**0.017**	23.80	2.14–264.24	**0.010**
	No bite to head/neck	1	1583	0.06%		Ref		
Other bite characteristics								
Number of bite wounds	Continuous	–	–	–	–	1.18	0.87–1.61	0.288
	One bite wound	0	127	0.0%	0.148	NE		
	Two bite wounds	1	1301	0.08%			–	–
	≥ three bite wounds	2	289	0.69%				
	1–2 bite wound	1	1428	0.07%	0.076	Ref	–	–
	> 2 bite wounds	2	289	0.69%		9.88	0.89–109.35	0.062
Documented suture◇	Suture	1/1	13/371	–	0.037◇	NE	–	–
	No suture	0/1	358/746	–				
Clothes interposed	Clothes interposed	0	440	0.0%	0.575	NE	–	
	No clothes interposed	3	1277	0.23%				
Documented wound care◇	Wound care	1/1	479/480	–	1.000◇	NE	–	–
	No wound care	0/0	267/267	–				
Dog status								
Spontaneous bite	Spontaneous bite	2	1447	0.14%	0.402	Ref		
	Provoked bite	1	270	0.37%		2.68	0.24–29.65	0.422
Sick-looking	Sick-looking dog	3	1638	0.21%	1.000	NE	–	–
	Non sick-looking dog	0	79	0.0%				
Identified owner	Identified owner	3	1443	0.21%	1.000	NE	–	–
	No identified owner	0	274	0.0%				
N persons bitten	Continuous	–	1720	–	–	0.50	0.09–2.62	0.410
	One person only	2	836	0.24%		NE		
	Two persons	1	410	0.24%	0.613		–	–
	≥ two persons	0	471	0.0%				
	One person only	2	836	0.24%	0.615	2.11	0.19–23.29	0.543
	Two persons or more	1	881	0.11%		Ref		
Dog outcome at first PEP	Dog died spontaneously	0	127	0.0%	1.000	NE	–	–
	Dog alive, put down or disappeared	3	1590	0.19%				
PEP characteristics								
Delay before PEP (days)	Continuous	–	–	–		0.25	0.03–2.16	0.208
	Same day (Day 0)	2	488	0.41%	0.219	NE		
	Between 1 and 6 days	1	1215	0.08%			–	–
	≥ 7 days	0	14	0.0%				
	Same day	2	488	0.41%	0.197	5.04	0.46–55.67	0.187
	One day or more	1	1229	0.08%		Ref		

(*continued on next page*)

Please cite this article as: A. Tarantola, S. Ly, M. Chan et al., Intradermal rabies post-exposure prophylaxis can be abridged with no measurable impact on clinical outcome in Cambodia, 2003–2014, Vaccine, https://doi.org/10.1016/j.vaccine.2018.10.054

Table 6 (*continued*)

Variable	Category	Rabies death	N alive	% death	p Fisher	Unadjusted Odds-ratio		p*
						Estimate	95% CI	
3 or 4 sessions	3 sessions	1	126	0.79%	0.206	6.25	0.57–71.43	0.134
	4 sessions or more	2	1591	0.12%		Ref		
ERIG	ERIG received	3	1665	0.18%	1.000	NE	–	–
	No ERIG	0	52	0.0%				

Abbreviations: PEP: post-exposure prophylaxis; ERIG: Equine rabies immunoglobulin; NE: Not estimable/not convergent; CI: 95% confidence interval; Ref: Reference category with OR value of 1.

* Likelihood ratio test p (p-values < 0.05 shown in bold).

** Non-exclusive categories as multiple bites on various anatomical sites are possible.

◇ These variables were poorly documented.

treating 33% more patients with the same vaccine quantity. In addition, this would spare patient resources and time spent for travel and loss of daily wages [11,14], as well as reduce patient crowding in high-throughput rabies clinics.

The inoculated RABV and ensuing rabies risk are neutralized by lavage, antisepsis and PEP within hours or days, while RABV remains located at the wound site [16]. Protection against rabies after a given bite is linked with short-term neutralization of RABV, not long-term antibody persistence. A three-session/one month pre-exposure intramuscular (IM) vaccination regimen has long been known to be effective [12,19]. Three-session ID regimens are included in the 2010 recommendations but these are also pre-exposure and last longer than one week at the time of writing [12]. A balance must be carefully struck between the much-desired abridgement of rabies PEP, the number of doses necessary to obtain an early protective immune response and the number of boosters. Patients in this observational study did not undergo serological monitoring due to sheer numbers and lack of funding. However laborious, *in natura* experiments such as our study in a cohort of patients exposed to dogs with confirmed rabies or by sick but untested dogs, stratified by PEP completion and RIG, offer the best real-life data reflecting clinical protection by PEP, especially abridged. A few authors have investigated the effectiveness of one-week PEP regimen with RIG, but only one was conducted in bite victims and none provided outcome data [20–22]. Aside from a very limited study documenting five IM PEP non-completers in Puerto Rico [23], our study is the largest to provide data on real-world clinical outcome in persons receiving abridged ID PEP after exposure to confirmed rabid or suspected but untested dogs in a rabies-endemic country. Other strengths of our study are that: data were prospectively collected (except outcome) with low loss to follow-up; an independent expert group attributed the cause of death to rabies; except for two variables (“owner identified” and “ERIG received”), patients who received 3 and 4+ PEP sessions were similar at baseline. Rabies cases die at home in many endemic rural areas but can be confirmed by verbal autopsy when virological diagnosis is lacking [11]. The callback system we established to document clinical outcome at six months for this IPC study has become routine. It will be used to guide future improvements in management by detecting protocol failures or deviation or to alert to otherwise ineffective PEP.

Rabies deaths despite PEP are extremely rare [24–26]. The probability of death due to rabies that we report among patients with confirmed rabies exposure is one-tenth of that published by Quiambao *et al.* (1.6%) in a smaller real-world cohort of 122 patients despite ID PEP and RIG following a bite by a rabid animal [27]. Another study after TRC-ID one-month PEP with RIG found zero deaths among 110 persons bitten by rabies-confirmed dogs [28]. In a large study in the Philippines, 3 In 2012, the full protocol changed from five to four 1 (1.68%) of 1839 rabies cases received PEP, of which eight also received RIG; one died of rabies despite full PEP and RIG [29]. Another study conducted in Pakistan documented two deaths among 2811 intradermal PEP recipients with Category II/III exposure [30]. These fatal cases had not completed PEP but the number of sessions completed is not mentioned. Furthermore, the dogs’ rabid status in the 2811 bite victims is undocumented. Such extremely rare rabies deaths are usually attributed to deviations from PEP protocols or direct delivery of RABV into nervous endings [30]. Sadly, our study documented three such fatal cases, which must be examined.

The fatal cases in our study suffered several bites to highly innervated areas of the body (head or finger), both factors known to be associated with transmission of rabies despite PEP. Cases 1 and 3 occurred after a short incubation period (19 days in each case) likely related to direct delivery of RABV into nervous endings, despite timely PEP including ERIG. The vaccine and RIG lots used in these patients were found effective by the manufacturer and/or were not associated with death in other confirmed PEP recipients following a bite by a dog with confirmed rabies. The death of Case 3 was highly likely, considering the extensive wounds to the head and unrecommended but necessary suturing. Case 2 is the only one to have died 39 days after ending the protocol after three sessions. Importantly, he had been bitten by a rabid dog in a different district of the same province but was managed for a bite to the head on the same day as Case 1, who also received ERIG and ID vaccine on the same day at IPC. We suspect that these two clustered deaths were therefore most likely due to a clinical management failure such as undetected wounds not being thoroughly infiltrated with ERIG in an extremely busy rabies prevention clinic with a total of 186 rabies PEP administered on that day [31].

Our field study has potential biases and limitations. First, this “natural experiment” may incur information bias by interviewing next-of-kin. The outcome, however, is survival or death and is less prone to bias. Second, verbal autopsies cannot fully replace virological confirmation and may underestimate deaths by misclassifying rabies cases with a paralytic presentation. Verbal autopsy tools, however, are particularly performant in the retrospective documentation of “furious” rabies which account for 80% of cases or more [32,33]. Furthermore, misclassification could have occurred in any PEP session subclass and bias would have been nonsystematic. Third, an additional 129 and 391 Phnom Penh residents bitten by rabid or sick-looking but untested dogs, respectively, were excluded based on early difficulties to trace them back. Unlike other residents, Phnom Penh residents are not tied to land or local industry, are highly mobile with looser social ties, therefore requiring a great amount of time to be traced, usually unsuccessfully. However, according to the differences existing between Phnom Penh and other residents exposed to rabid dogs (Supplementary Table ST1), the proportion of Category III bites was significantly higher among those residing outside Phnom Penh. Furthermore –

Please cite this article as: A. Tarantola, S. Ly, M. Chan et al., Intradermal rabies post-exposure prophylaxis can be abridged with no measurable impact on clinical outcome in Cambodia, 2003–2014, Vaccine, https://doi.org/10.1016/j.vaccine.2018.10.054

as happened for Case 3 – our team would have been informed of suspected rabies deaths, IPC being widely identified as the expert center for rabies in Cambodia. Our strategy to exclude Phnom Penh residents was probably more prone to underestimating the efficacy of PEP in any PEP category, abridged or otherwise. Fourth, follow up was at least six months, potentially missing cases which may have died later. The present study, however, was undertaken between late 2013 and 2016, by which time >73% of our retrospectively documented patients had over one year's follow-up. Furthermore, rabies incubation is usually shorter than six months [34]: In an unrelated 1998–2007 study, the median incubation period in 44 Cambodian human rabies cases – all unvaccinated – was 60 days, with a range of 30–100 days [10]. In any case, such evaluation bias would have been nonsystematic across PEP session categories. Fifth, loss to follow-up may have omitted patients who died of rabies, underestimating the risk of PEP failure. The loss to follow-up was low – especially among rabies-exposed patients (6.35%) – because our center collects data in a timely fashion, made important efforts to trace back and call patients back after six months starting in 2013 and residents of rural areas often have stable situations. Comparisons between those traced back and those lost to follow-up show that the latter had more frequent risk factors associated with higher rabies transmission risks (Supplementary Table ST2) and longer time elapsed since PEP. Had loss to follow-up led to undetected rabies deaths, these could have occurred in any PEP category, abridged or otherwise. Sixth, the use of ERIG (prioritized in case of confirmed exposure to rabies and/or a bite to the head/neck and/or fingers) may have brought the various vaccine protocols' differences towards the null, overestimating the effectiveness of a 3-sessions regimen. This may be the case, but it would have been unethical to do otherwise. Of note, 53 and 165 patients bitten by confirmed rabid and rabid or untested dogs, respectively, received no ERIG (shortage) and did not develop rabies. Finally, our study suffers from limited statistical power, estimated *post-hoc* at 49%. Ours is the largest series worldwide to our knowledge and denominators are ample but PEP is so effective that deaths were rare, as we were hoping.

5. Conclusion

Our real-life study could not document a decrease in effectiveness of a three ID sessions/one week PEP regimen of two ID 0.1 mL doses at days 0, 3 and 7 – with or without RIG – compared to the time-proven, highly effective four-session/one-month regimen. As suggested for IM regimens [23], our findings therefore support the abridgment of the TRC to an IPC protocol at no detectable added risk to patients, with the limitation of study power. The World Health Organization endorsed this regimen in its 2018 recommendations as the first one-week and dose-sparing PEP regimen [35]. Post-PEP monitoring is continuing at IPC and should be implemented worldwide, especially during the initial phases following the introduction of this regimen. Adopting the IPC regimen will significantly reduce cost for vaccine, repeat transportation and accommodation and other indirect vaccination costs and share vaccine doses more equitably by reducing vaccine use in patients.

Funding

Institut Pasteur.

Declaration of interest

Dr. Philippe Buchy is a former Head of Virology at Institut Pasteur du Cambodge and is currently an employee of GSK Vaccines.

Acknowledgements

We wish to acknowledge participating patients in Cambodia, the very wonderful (''AbFab'') team at IPC and the members of the independent Expert panel: Thiravat Hemachudha; Reeta Subramaniam; and Henry Wilde. We thank Andrew Lover for statistical insights and Direction Internationale of Institut Pasteur, Paris for funding and support for the RESIST program through an ACIP grant.

References

[1] Hampson K, Coudeville L, Lembo T, Sambo M, Kieffer A, Attlan M, et al. Estimating the global burden of endemic canine rabies. PLoS Negl Trop Dis 2015;9(4):e0003709. Carvalho MS, editor.
[2] Weyer J, Msimang-Dermaux V, Paweska JT, le Roux K, Govender P, Coertse J, et al. A case of human survival of rabies, South Africa. South Afr J Infect Dis 2016;31(2):1–3.
[3] Tarantola A. Four thousand years of concepts relating to rabies in animals and humans, its prevention and its cure. Trop Med Infect Dis. 2017;2(2):5.
[4] Putra AAG, Hampson K, Girardi J, Hiby E, Knobel D, Mardiana IW, et al. Response to a rabies epidemic, Bali, Indonesia, 2008–2011. Emerg Infect Dis 2013;19(4):648–51.
[5] Windiyaningsih C, Wilde H, Meslin FX, Suroso T, Widarso HS. The rabies epidemic on Flores Island, Indonesia (1998–2003). J Med Assoc Thail Chotmaihet Thangphaet. 2004;87(11):1389–93.
[6] Tohma K, Saito M, Demetria CS, Manalo DL, Quiambao BP, Kamigaki T, et al. Molecular and mathematical modeling analyses of inter-island transmission of rabies into a previously rabies-free island in the Philippines. Infect Genet Evol J Mol Epidemiol Evol Genet Infect Dis 2016;38:22–8.
[7] Asian Development Bank. Cambodia;country poverty analysis 2014. [Internet]. Oakland: O Books Sun & Moon. Available from: http://public.eblib.com/choice/publicfullrecord.aspx?p=4453753 [cited 2018 Sep 21].
[8] National Institute of Statistics/Cambodia. Cambodia demographic and health survey 2014 [Internet]. Phnom Penh: Directorate General for Health, Cambodia; 2015. Available from: http://www.webcitation.org/72sWXhK0G [cited 2018 Sep 21].
[9] Ponsich A, Goutard F, Sorn S, Tarantola A. A 6-months descriptive study of dog bites in rural Cambodia. Acta Trop 2016;160:62–7.
[10] Ly S, Buchy P, Heng NY, Ong S, Chhor N, Bourhy H, et al. Rabies situation in Cambodia. PLoS Negl Trop Dis. 2009;3(9):e511.
[11] Tarantola A, Ly S, In S, Ong S, Peng Y, Heng NY, et al. Rabies vaccine and rabies immunoglobulin in Cambodia: use and obstacles to use. J Travel Med 2015;22(5):348–52.
[12] World Health Organization. WHO position paper on rabies. Wkly Epidemiol Rec 2010;85(32):309–20.
[13] Dodet B, Africa Rabies Bureau (AfroREB). The fight against rabies in Africa: from recognition to action. Vaccine 2009;27(37):5027–32.
[14] Tarantola A, Blanchi S, Cappelle J, Ly S, Chan M, In S, et al. Rabies Postexposure Prophylaxis (PEP) noncompletion after dog bites: estimating the unseen to meet the needs of the underserved. Am J Epidemiol 2018;187(2):306–15.
[15] Duong V, Tarantola A, Ong S, Mey C, Bourhy H, Dussart P, et al. Laboratory diagnostics in dog-mediated rabies – an overview of performance and a proposed strategy in various settings. Int J Infect Dis 2016;46:107–14.
[16] World Health Organization. WHO expert consultation on rabies: second report [Internet]. Geneva, Switzerland; 2013. (WHO technical report series). Report No.: 982. Available from: http://www.webcitation.org/72sWSnja1.
[17] Hirji KF, Tan SJ, Elashoff RM. A quasi-exact test for comparing two binomial proportions. Stat Med 1991;10(7):1137–53.
[18] Agresti A. A survey of exact inference for contingency tables. Stat Sci. 1992;7(1):131–53.
[19] Ren J, Yao L, Sun J, Gong Z. Zagreb Regimen, an abbreviated intramuscular schedule for rabies vaccination. Clin Vaccine Immunol 2015;22(1):1–5.
[20] Shantavasinkul P, Tantawichien T, Wilde H, Sawangvaree A, Kumchat A, Ruksaket N, et al. Postexposure rabies prophylaxis completed in 1 week: preliminary study. Clin Infect Dis Off Publ Infect Dis Soc Am 2010;50(1):56–60.
[21] Khawplod P, Wilde H, Tepsumethanon S, Limusanno S, Tantawichien T, Chomchey P, et al. Prospective immunogenicity study of multiple intradermal injections of rabies vaccine in an effort to obtain an early immune response without the use of immunoglobulin. Clin Infect Dis Off Publ Infect Dis Soc Am 2002;35(12):1562–5.
[22] Narayana A, Manoharan A, Narayan MS, Kalappa SM, Biligumba G, Haradanahalli R, et al. Comparison of safety and immunogenicity of 2 WHO prequalified rabies vaccines administered by one week, 4 site intra dermal regimen (4-4-4-0-0) in animal bite cases. Hum Vaccines Immunother 2015;11(7):1748–53.
[23] Robertson K, Recuenco S, Niezgoda M, Garcia EJ, Rupprecht CE. Seroconversion following incomplete human rabies postexposure prophylaxis. Vaccine 2010;28(39):6523–6.
[24] Giesen A, Gniel D, Malerczyk C. 30 years of rabies vaccination with Rabipur: a summary of clinical data and global experience. Expert Rev Vaccines 2015;14(3):351–67.

Please cite this article as: A. Tarantola, S. Ly, M. Chan et al., Intradermal rabies post-exposure prophylaxis can be abridged with no measurable impact on clinical outcome in Cambodia, 2003–2014, Vaccine, https://doi.org/10.1016/j.vaccine.2018.10.054

[25] Toovey S. Preventing rabies with the Verorab vaccine: 1985–2005 twenty years of clinical experience. Travel Med Infect Dis 2007;5(6):327–48.
[26] Wilde H, Sirikawin S, Sabcharoen A, Kingnate D, Tantawichien T, Harischandra PA, et al. Failure of postexposure treatment of rabies in children. Clin Infect Dis Off Publ Infect Dis Soc Am 1996;22(2):228–32.
[27] Quiambao BP, DyTioco HZ, Dizon RM, Crisostomo ME, Laot TM, Teuwen DE. Rabies post-exposure prophylaxis in the philippines: health status of patients having received purified equine F(ab')2 fragment rabies immunoglobulin (Favirab). PLoS Negl Trop Dis 2008;2(5):e243.
[28] Quiambao BP, Dimaano EM, Ambas C, Davis R, Banzhoff A, Malerczyk C. Reducing the cost of post-exposure rabies prophylaxis: efficacy of 0.1 ml PCEC rabies vaccine administered intradermally using the Thai Red Cross post-exposure regimen in patients severely exposed to laboratory-confirmed rabid animals. Vaccine 2005;23(14):1709–14.
[29] Dimaano EM, Scholand SJ, Alera MTP, Belandres DB. Clinical and epidemiological features of human rabies cases in the Philippines: a review from 1987 to 2006. Int J Infect Dis IJID Off Publ Int Soc Infect Dis 2011;15(7):e495–9.
[30] Salahuddin N, Gohar MA, Baig-Ansari N. Reducingcost of rabies post exposure prophylaxis: experience of a tertiary care hospital in Pakistan. PLoS Negl Trop Dis 2016;10(2):e0004448. Rupprecht CE, editor.
[31] Wilde H. Failures of post-exposure rabies prophylaxis. Vaccine 2007;25 (44):7605–9.
[32] Chandramohan D, Maude GH, Rodrigues LC, Hayes RJ. Verbal autopsies for adult deaths: their development and validation in a multicentre study. Trop Med Int Health TM IH 1998;3(6):436–46.
[33] Department of Measurement and Health Information Systems. WHO technical consultation on verbal autopsy tools. Talloires, France, 2–3 November 2004: final report. [Internet]. Talloires: World Health Organization; 2005 Apr [cited 2014 Sep 30], p. 45. Available from: http://www.webcitation.org/71jUI4CA0.
[34] Anderson LJ, Nicholson KG, Tauxe RV, Winkler WG. Human rabies in the United States, 1960 to 1979: epidemiology, diagnosis, and prevention. Ann Intern Med 1984;100(5):728–35.
[35] World Health Organization. Rabies vaccines: WHO position paper. Wkly Epidemiol Rec 2018;2018(93):201–20.

Please cite this article as: A. Tarantola, S. Ly, M. Chan et al., Intradermal rabies post-exposure prophylaxis can be abridged with no measurable impact on clinical outcome in Cambodia, 2003–2014, Vaccine, https://doi.org/10.1016/j.vaccine.2018.10.054