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Impact of the switch from four to three intradermal rabies post-exposure prophylaxis sessions in patients bitten by dogs: A cost-consequence analysis from the patients' perspective

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ABSTRACT

The annual incidence of rabies deaths has been estimated in Cambodia at nearly 5.8/100,000 person-years. The cost of post exposure prophylaxis (PEP) and travel is potentially a significant barrier for exposed patients and their families, although safety nets are in place to provide the prophylaxis at no cost for low-income families. A decision-tree model was built to estimate changes in the costs from the patients' perspective and the survival outcomes of the Institut Pasteur du Cambodge (IPC) rabies PEP regimen after the switch from the Thai Red Cross (TRC) rabies PEP regimen in patients exposed to WHO category II or III bites by dogs. Derived from the IPC database, data included the trajectory of 203,497 patients, 1412 called-back patients and economic data on 201 patients. Uncertainty was addressed using one-way and probabilistic sensitivity analyses. Compared to the TRC regimen, the IPC regimen was cheaper and equally effective in patients with category II bites. In patients with category III bites, the IPC regimen was cheaper and its modeled probability of survival was 0.04% (95% CI, −0.12%; 0%) lower than the TRC regimen. However, the mortality rate was very low and the causes of death were uncertain. The data available may have lacked power to be able to statistically significantly tell apart the difference between genuine PEP failure and incorrect PEP administration, in the three versus the four-PEP sessions.

1. Introduction

Rabies is a viral meningoencephalitis causing an estimated 59,000 human deaths each year [1]. In Cambodia, the incidence of dog bites is estimated at 4.84/100 person-years [2] and the incidence of human rabies deaths at 5.8/100,000 [3]. Transmission is inconstant even after a bite from a rabid dog but rabies is always fatal after symptoms appear [4]. Rabies is prevented if the victim receives timely and adequate post-exposure prophylaxis (PEP) before developing symptoms.

According to the WHO, rabies exposures can be of: 1) category 1 including touching or feeding animals, animal licks on intact skin (no exposure), 2) category 2 including nibbling of uncovered skin, minor scratches or abrasions without bleeding (exposure), 3) category 3 including single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks, exposures due to direct contact with bats (severe exposure) [5].

There is however an issue of inappropriate compliance to the full course of PEP sessions related either to the constraints and financial negative incentives to patients who need to travel (pay travel costs and accommodation) and lose a day of paid employment for each session or to the discontinuation of sessions when the dog is found non rabid [6]. According to Changalucha J. et al., nearly 15% of probable rabies-exposed persons in Tanzania did not receive PEP due to cost barriers or vaccine shortages [7].

The hypothesis of the Institut Pasteur du Cambodge (IPC) was that reducing the number of PEP sessions would reduce cost to individuals while not reducing the effectiveness of prevention after a bite, through improved compliance and care-seeking and thus potentially better cost-effectiveness. Tarantola et al. [8] conducted a case-control study on 3318 Cambodians who received intradermal Verocell-based vaccine PEP

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with 3 or 4+ sessions after a bite by a rabid or sick-looking but untested dog between 2003 and 2014 and concluded that the four-PEP sessions could be reduced to three sessions without additional risk to patients. A subsequent serological study by the same team proved that conferred protection was equivalent [9]. The number of PEP sessions was reduced from four to three at the Institut Pasteur du Cambodge (IPC), and the new recommendation validated by WHO [5,6]. The full description of the PEP process is presented in Appendix A.

While reduction in the number of sessions should reduce proportionally costs to both healthcare providers and patients, the real impact of a three-session regimen on compliance and out-of-pocket cost was unknown as few studies have examined the out-of-pocket expenses faced by families [10]. Additionally, the real-world compliance with the required number of sessions, either 4 or 3, affects both the costs and outcomes. Our objective was to measure how the switch from 4 to 3 PEP sessions would affect both the cost to PEP seeking individuals and the effectiveness of prevention (probability of survival without rabies), and to estimate the cost-effectiveness of the IPC regimen (three ID sessions) compared to the Thai Red Cross (TRC) regimen (four ID sessions) in unvaccinated persons bitten by dogs, whichever the dog's rabies status.

2. Methods

We developed a decision-tree to model the trajectory, costs and clinical outcomes for patients with category II bites and category III bites. A decision tree presents the disease outcomes under different treatment assumptions; the likelihood of each outcome and the associated costs can be represented on the tree-like diagram. We compared the IPC regimen (new strategy) vs. TRC regimen (reference strategy) (Fig. 1).

For each comparison, we calculated the effectiveness (probability of survival without rabies) and the costs. All inputs for the model were derived from patient-level data collected prospectively by the IPC.

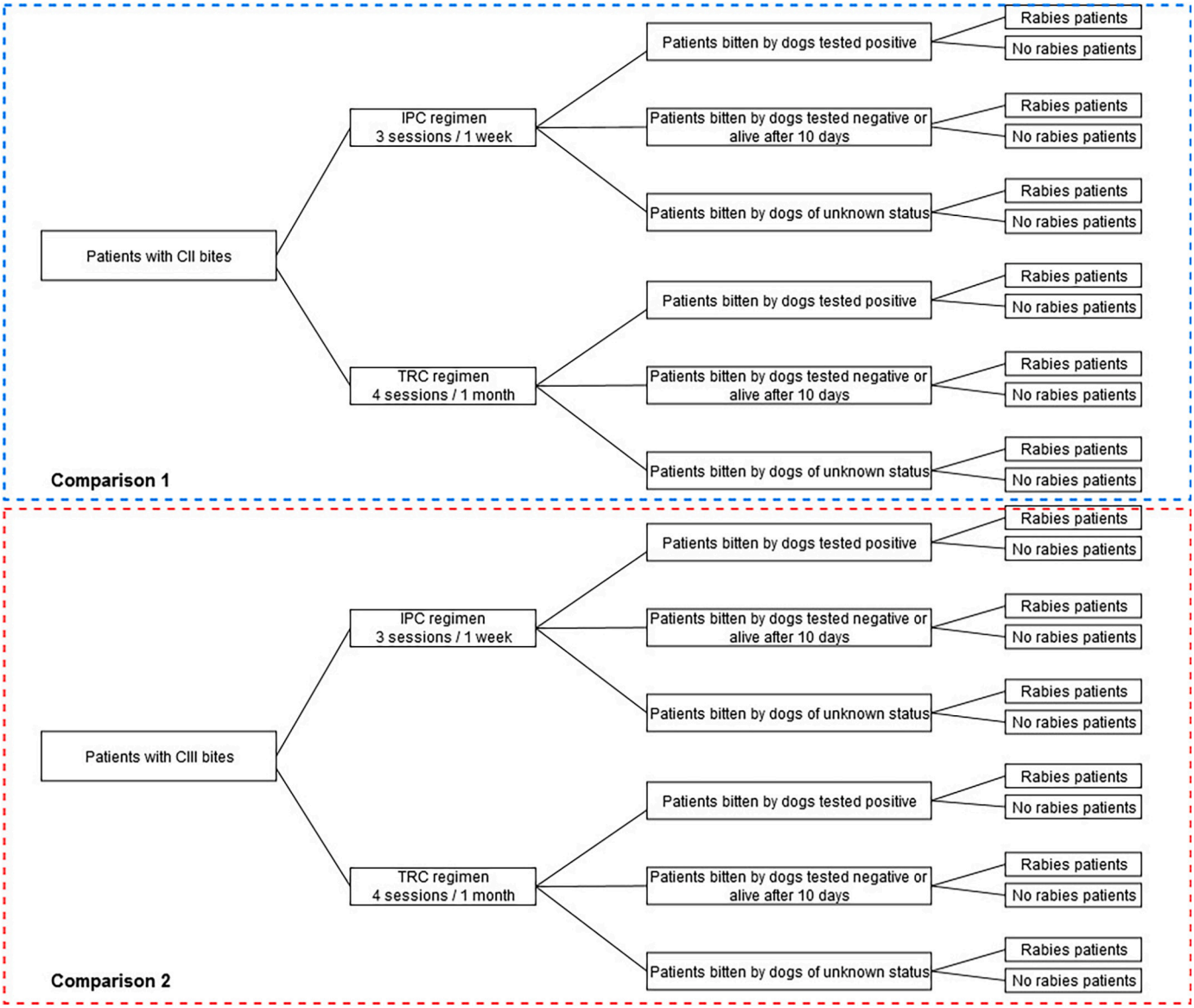

Fig. 1. Decision tree simulating patient trajectory of unvaccinated patients referring to the IPC for PEP after categories II/III bites, with or without ERIG. Comparison 1 compares the IPC regimen vs. TRC regimen in patients with category II bites. Comparison 2 compares the IPC regimen vs. TRC regimen in patients with category III bites.
Notes. *Tested negative or alive at 10 days.

2.1. Data sources and resource utilization

Three databases of the IPC information system used for data inputs are summarized in Table 1 and detailed in Appendix B.

2.2. Key assumptions

1. Patients who died before PEP protocol completion could not be formally allocated to either PEP regimen and were therefore excluded from the analysis;
2. Superficial and deep injuries were considered category II and III bites [5], respectively;
3. All patients whose dogs had tested negative or remained in good health ten days after the exposure were considered non-rabid;
4. The outcome data for patients bitten by non-sick-looking dogs of unknown status were imputed by frequency of rabies-related deaths in patients bitten by sick-looking dogs of unknown status (worst case scenario);
5. The rabies virus had not been transmitted if no symptoms appeared six months after the exposure.

2.3. Effectiveness

The primary effectiveness endpoint was the probability of survival without rabies despite PEP with three compared to four PEP sessions. Over the study period, three deaths were attributed to rabies by an external expert panel [8]. All patients had initiated PEP with equine rabies immunoglobulin (ERIG) within the first 24 h after a category III bite on the upper extremities or head by rabid confirmed dogs. Among these, two patients died before the planned date of the fourth PEP session.

2.4. Costs

The economic evaluation was conducted from the patient's perspective, as out-of-pocket expenses represent a significant financial burden and possible disincentive to seek PEP.

Most IPC patients did not undergo free-of-charge wound cleansing, sometimes due to delays following the bite or because most had cleansed the wound before referral. Patients with complicated wounds were referred to hospitals after PEP. Other costs were faced by patients who received wound care before PEP at another treatment facility. Patients' financial contribution to ID rabies PEP (excluding the cost of ERIG) at IPC has been set at US$15 since February 2018. Independently of the number of sessions, this flat fee was paid in full during the first visit to avoid becoming a disincentive for ulterior PEP sessions. When required, ERIG represented an additional cost of $32 for patients of 15 years of age or younger and $45 for others. Patients were encouraged to bring the dog's head to the IPC laboratory for cost-free rabies testing. The mean cost of one round trip was the total cost of transport reported by patients or guardians for the three sessions divided by three and adjusted on the place of residence in or outside Phnom Penh. Patients who had to reside near IPC during the first week of rabies PEP also faced costs for accommodation. There was no assessment of costs associated with care for patients with clinical rabies, since these in Cambodia unfortunately rapidly die at home soon after symptoms appear.

Indirect costs were earnings foregone (cost of time not in work) to refer for rabies PEP and were estimated from the patient's or relative's net monthly income. We considered a loss of income equivalent to 0.5 days per PEP session for a round trip to IPC of three hours or less, and one day otherwise.

All costs were expressed in American dollars ($) at 2018 values.

2.5. Sensitivity analyses

We performed a probabilistic sensitivity analysis to address the

Table 1
Summarized description about the three databases of the IPC information system used for data inputs*.

	Database 1 Socio-demographic and clinical characteristics of all IPC patients, completed prospectively at each PEP session	Database 2 Clinical outcomes of all patients referred to IPC and included in the call-back procedure	Database 3 Socio-demographic, clinical and economic characteristics of all patients referred to IPC for the third session
No. Patients included in this study	203,497	1711	201
Dates of data collection	January 2003 – December 2014	June 2011 – July 2016	21 August 2018 – 6 September 2018
Eligibility criteria	Not previously immunized patients referred to IPC for PEP after suffering a category II or III bite by dogs	Patients included in Database 1 after suffering a category II or III bite by rabid confirmed dogs or sick-looking but untested dogs; Patients received three or four PEP-sessions and were followed up after at least 6 months	Not previously immunized patients referred to IPC for the third session (day 7) PEP after suffering a category II or III bite by dogs
Exclusion criteria	Missing data regarding previous rabies vaccination, exposure mode, number of sessions, type of wound or age	Phnom Penh residents were excluded since the first attempts failed to identify any of these highly mobile persons	
Person entering information	Professionals	Professionals	Patients
Information available (patient level)	Characteristics of the patient (age, gender, district), of the accident (date of the accident, mode of exposure, superficial or deep wound, surface of contact, bleeding), of the animal (species, animal behavior, types of aggression, dog's status after 10 days, result of the laboratory test), of the management (local care, anti-rabies serum, type of vaccine, reason for non-compliance in PEP)	Clinical outcomes: healthy, sick, dead or lost to follow-up	Same information available as in the database 1, cost of transport and accommodation, travel time, number of relatives and net monthly income by patient or relative
Input extracted for the model	Age category, categories II/III bites, dog's status: non-rabid, rabid dog, unknown status, number of sessions, Pr of receiving wound cleaning at IPC†, Pr of receiving ERIG by age category†, Probability of being a Phnom Penh resident	Clinical outcomes: Healthy; Sick; Dead or Lost to follow-up	Out-of-pocket costs, Pr of receiving wound cleaning outside the IPC, probability of being a Phnom Penh resident

* ERIG, equine rabies immunoglobulin; IPC, Institut Pasteur du Cambodge; PEP, post-exposure prophylaxis; Pr, Probability.

† Calculated from patients referred to IPC in 2014 because this variable was poorly documented before 2013.

uncertainty of the model parameters on costs and effectiveness. We used beta distribution for the parameters corresponding to a probability, where α and β are the number of times the event is observed and unobserved, respectively. Gamma distribution for costs was parameterized using the method of moments given the sample mean and the sample variance. Uncertainty in all model parameters was assessed using a Monte Carlo simulation, sampling 10,000 random values from input distributions - rabies despite PEP being a very rare event - to take into account the common uncertainty of all model parameters.

In addition, we assumed for a deterministic sensitivity analysis that 1) PEP was provided for free under the Global Alliance for Vaccines and Immunization (GAVI) scheme and 2) that all patients lost to follow-up in database 2 were deceased.

Statistical analyses were performed with R statistical software 3.4 [11].

3. Results

Distributions of baseline patient characteristics selected in the three databases and inputs are presented in Table 2. Out of 1711 patients who received three or four PEP sessions after a bite by a dog with confirmed or suspected rabies and were included in the call-back procedure 6 months or more after the bite, 318 received the IPC regimen and 1393 received the TRC regimen. For each of the two regimens, the number of patients lost to follow-up was 78 (24.6%) and 221 (15.9%) respectively. The comparison of patient characteristics between lost to follow-up and followed-up is presented in Table 3.

The model parameters for trajectory, clinical outcomes and costs are presented in Table 4.

3.1. Base case analysis

No deaths were reported in patients who received the IPC regimen (three-PEP sessions) after sustaining a Category II bite, and the mean cost per patient with a Category II bite was $44.5 (Table 5). No deaths were reported in the TRC group (four-PEP sessions) after a Category II bite, and the mean cost was $45.9 per patient. The reduction from four to three-PEP sessions resulted in a cost reduction of $1.4 per patient, ranging from $9.0 for a confirmed rabid dog or a dog of unknown status to 0$ for a confirmed non-rabid dog. The IPC regimen was therefore cheaper and as effective as the TRC regimen for Category II bites.

The proportion of survival without rabies was 99.96% in patients who received an IPC regimen after a Category III bite, with a mean cost per patient of $75.5 (Table 5). No deaths were reported among TRC regimen recipients after a Category III bite in our study, with a mean cost per patient of $76.8. The reduction from four to three-PEP sessions resulted in a cost reduction of $1.3 per patient, ranging from $8.9 for a confirmed rabid dog or a dog of unknown status to 0$ for a confirmed non-rabid dog, and 0.04% decrease in the probability of survival without rabies. The IPC regimen was therefore cheaper but less effective than the TRC regimen.

Regardless of the bite category, only 15% of patients were actually concerned by the reduction from 4 to 3 sessions, because patients with a bite by a confirmed non-rabid dog discontinued TRC PEP before the fourth session (Table 5).

Assuming that the 203,497 patients referred to IPC for PEP between 2003 and 2014 had all received and completed a TRC regimen, the total patient cost would have been $10,619,104. The use of the IPC regimen over the same period would have represented a cost of $10,334,873 for patients, a saving of $284,231 compared to the previous situation.

Table 2
Distribution of baseline patient characteristics and inputs in the three databases*.

	Database 1 n = 203,497	Database 2 n = 1711	Database 3 n = 201
Age - mean (± sd)	21.4 (± 18.4)	23.7 (± 18.7)	21.2 (±17.7)
Child (<16 years old) - No. (%)	106,255 (52.2)	807 (47.2)	100 (49.8)
Male - No. (%)	106,477 (52.3)	965 (56.4)	103 (51.2)
Phnom Penh Residents - No. (%)	100,640 (49.7)	NA	110 (54.7)
Bite characteristics			
Bite category - Category CIII - No. (%)	41,463 (20.4)	350 (20.5)	10 (5.0)
Documented wound care at IPC† – No. (%)	21,695 (10.7)	441 (25.8)	12 (6.0)
Documented wound care outside IPC† – No. (%)	NA	NA	41 (21.7)
Dog status			
Spontaneous bite - No. (%)	144,660 (71.1)	1361 (79.5)	117 (58.2)
Sick looking - No. (%)	5244 (2.6)	1669 (97.5)	12 (6.0)
PEP characteristics			
ERIG received - No. (%)	6550 (3.2)	1551 (90.6)	13 (6.5)
PEP sessions - mean (± sd)	3.2 (± 0.8)	3.8 (± 0.4)	3 (–)
1–2 sessions	7808 (3.8)	0 (0)	0 (0)
3 sessions	167,404 (82.3)	318 (18.6)	201 (100)
4 sessions	10,878 (5,3)	1393 (81.4)	0 (0)
5 sessions or more	17,407 (8.6)	0 (0)	0 (0)
Delay before PEP (days) - mean (± sd)	2.0 (± 2.2)	2.2 (± 4.2)	1.5 (± 1.4)
Same day (Day 0) - No. (%)	37,347 (18.4)	299 (17.5)	51 (25.4)
After 1–6 days - No. (%)	162,687 (79.9)	1350 (78.9)	147 (73.1)
After one week (>Day 6) - No. (%)	3643 (1.7)	62 (3.6)	3 (1.5)
Economic characteristics			
Number of relatives - No. (%)			
• Child	NA	NA	1.3 (± 0.5)
• Adult	NA	NA	0.4 (± 0.5)
Travel time to IPC per session (hours) - mean (± sd)	NA	NA	2.1 (± 1.8)
Wound care outside IPC (in USD) - mean (± sd) ‡	NA	NA	5.1 (± 6.1)
Net income (per month in USD) among >17 years old - mean (± sd)	NA	NA	162 (± 139)
Accommodation for complete PEP (in USD) - mean (± sd)	NA	NA	0.6 (± 4.7)
Transportation per session (in USD) - mean (± sd)	NA	NA	4.6 (± 5.8)
Income loss among adult patients per session (in USD) - mean (± sd)	NA	NA	3.0 (± 2.5)
Income loss among relatives of child patients per session (in USD) - mean (± sd)	NA	NA	4.7 (± 5.2)
Income loss among relatives of adult patients per session (in USD) - mean (± sd)	NA	NA	1.0 (± 2.0)

* ERIG, equine rabies immunoglobulin; IPC, Institut Pasteur du Cambodge; PEP, post-exposure prophylaxis; NA, not applicable.

† This variable was poorly documented before 2013.

‡ If wound care was not performed at the IPC.

Table 3
Comparison between patients lost to follow-up and those followed-up included in the call-back procedure 6 months or more after the bite - Distribution of patient characteristics*.

	Follow-up patients n = 1412	Patients lost to follow-up n = 299	*P*-value
Age - mean (± sd)	24.2 (± 18.9)	21.3 (± 17.7)	0.01
Child (<16 years old) - No. (%)	649 (46.0)	159 (52.8)	0.03
Male - No. (%)	793 (56.2)	172 (57.5)	0.67
Bite characteristics			
Bite category - Category CIII - No. (%)	296 (21.0)	54 (18.1)	0.26
Documented wound care at IPC† – No. (%)	373 (26.4)	68 (22.7)	0.19
Dog status			
Spontaneous bite - No. (%)	1143 (80.9)	218 (72.9)	<0.01
Sick looking - No. (%)	38 (2.7)	4 (1.3)	0.17
Dog confirmed rabies - No. (%)	581 (41.1)	39 (13.0)	<0.01
Dog of unknow status - No. (%)	831 (58.9)	260 (87.0)	
PEP characteristics			
ERIG received - No. (%)	1313 (93.0)	238 (79.6)	<0.01
PEP regimen	3.8 (± 0.4)	3.7 (± 0.4)	<0.01
• *IPC regimen* - No. (%)	*240 (17.0)*	*78 (26.1)*	<0.01
• *TRC regimen* - No. (%)	*1172 (83.0)*	*221 (73.9)*	
Year of PEP - median (IQR)	2012 [2011–2014]	2011 [2008–2013]	<0.01
Delay before PEP (days) - No. (%)	2.0 (± 3.0)	3.1 (± 7.7)	<0.01
Same day (Day 0) - No. (%)	259 (18.3)	40 (13.4)	0.02
After 1–6 days - No. (%)	1108 (78.5)	242 (80.9)	
After one week (>Day 6) - No. (%)	17 (5.7)	45 (3.2)	
Follow-up			
Delay until callback (months) – mean (± sd)	30.4 (± 26.6)	52.1 (± 40.9)	<0.01
>12 months - No. (%)	1074 (76.1)	284 (95.0)	<0.01

* ERIG, equine rabies immunoglobulin; IPC, Institut Pasteur du Cambodge; IQR, interquartile range; PEP, post-exposure prophylaxis; NA, not applicable.
† This variable was poorly documented before 2013.

3.2. Sensitivity analyses

The probabilistic sensitivity analyses showed that the IPC regimen for patients with a category II bite was always cheaper and equally effective. The differences in terms of probability of survival between the IPC regimen and TRC regimen were 0 for a cost difference of $-1.4 (95% CI, $-2.0; $-0.8). With the IPC regimen, the probability of survival was lower by 0.04% (95% CI, −0.12%; 0%) and the cost lower by $1.4 (95% CI, $-2.7; $-0.1) for full rabies PEP.

When removing the cost of PEP under the assumption that it would be provided for free, the mean cost per patient with a category II bite was $29.5 in the IPC regimen and $30.9 in the TRC regimen. With a category III bite, these figures were $60.5 and $61.8.

When assuming that all patients lost to follow-up were deceased, the probability of survival was 94,64% in patients who received an IPC regimen after a Category II bite compared to 96,81% with the TRC regimen, i.e., a lower probability of survival of 2.17%. In patients with a category III bite, the percentage of survival was 95.36% with the IPC regimen compared to 96.87% with the TRC regimen, i.e., a lower probability of survival of 1.51%.

4. Discussion

Our cost-consequence analysis showed that the IPC regimen (three-PEP sessions) was cheaper for patients and associated with the same rabies incidence in patients with category II bites compared to the TRC regimen (four-PEP sessions). We estimated a mean out-of-pocket cost per patient of $44.5 with the IPC regimen compared to $45.9 with the TRC regimen, i.e., a mean saving of $1.4. In patients with category III bites, IPC regimen was cheaper but was less effective with a lower probability of survival of 0.04% (95%CI, −0.12%; 0%). The mean saving for full rabies PEP was $1.3 per patient. Table 5 shows that the reduction in costs between TRC and IPC regimens differed by dog's status and bite category. In short, for dogs confirmed non rabid, compliance with the 4-session TRC regimen was non-existent, thereby reducing the TRC cost to the level of IPC costs. For the 15% of patients who actually had one fewer session with the IPC regimen, the out-of-pocket costs were reduced by $9.0 (a significant savings relative to the mean net monthly income of $162 for individuals over 17 years of age).

The main strength of our study is the robustness of the results, which was possible due to the use of large databases, including the trajectory of 203,497 patients, 1412 follow-up patients and economic data in 201 patients.

We have identified the following limitations.

Firstly, our study investigated association, not causation. All three fatal cases had initiated PEP with ERIG within the first 24 h after the exposure. One rabies case in 2011 suffered several bites and massive inoculum to the highly innervated areas of the head and upper extremities. The two other rabies deaths which occurred throughout this 11-year period are highly suspected of having received inadequate PEP as they were clinically managed on the same day in 2008. Two of these three fatal cases died before completing the protocol and were not taken into account in our analysis. The remaining fatal case discontinued PEP after 3 sessions, died at day 46 and is the only case included in our analysis. Furthermore, there were no spontaneously reported deaths among 5541 IPC patients without clinical follow-up who discontinued PEP after 3 sessions following a bite by an untested dog not available for observation. The mortality rate was very low and the causes of death were uncertain. The data available may have lacked power to distinguish statistically significantly the difference between genuine PEP failure and incorrect PEP administration, in the three versus the four-PEP sessions.

Secondly, the imbalance between the low number of clinically-documented patients who discontinued PEP after three sessions and the number of patients who received the then WHO-recommended four PEP sessions (240 vs. 1172). As IPC switched to the three-session “IPC regimen” in May 2018 (no reported deaths since full implementation), a large patient dataset will soon be available for further analysis.

Thirdly, the economic analysis in the 201 patients may have been limited by the lack of exhaustiveness of economic data. Indeed, it was not possible to estimate costs by bite category since only ten (5.0%) interviewed patients had sustained a category III bite. However, we can assume that the most distant residents will have greater interest to seek PEP after a severe bite, thereby incurring higher out-of-pocket costs. We may therefore have underestimated the cost to patients with a category III bite.

Fourthly, as the incubation period of rabies varies from three months to one year, it is possible that some rabies deaths may have gone undetected. However, 87% and 74% of patients bitten by sick-looking and untested dogs or by confirmed rabid dogs, respectively, were successfully called back after at least one year after receiving the IPC regimen [8].

Fifthly, among 318 and 1393 patients who received three or four PEP sessions after suffering a category II or III bite by rabid confirmed dogs or sick-looking but untested dogs and vaccinated with Verorab®, only 240 (75%) and 1172 (84%) was successfully called-back. However, we performed a sensitivity analysis assuming that all patients lost to follow-

Table 4
Selected model parameters: Base case values and distributions used in the probabilistic sensitivity analysis*.

	Regimen Comparison 1: Patients with Category II bites		Regimen Comparison 2: Patients with Category III bites		Years
	Base case (%)	Distributions	Base case (%)	Distributions	
% of IPC patients bitten by confirmed rabid dogs	0.91	Beta [α- 1479; β- 160,555]	1.45	Beta [α- 600; β- 40,863]	[2003–2014]
% of IPC patients bitten by confirmed non-rabid dogs†	84.28	Beta [α- 136,566; β- 23,989]	84.83	Beta [α- 35,173; β- 5690]	[2003–2014]
% of IPC patients bitten by dogs of unknown status	14.80	–	13.72	–	[2003–2014]
Patients bitten by confirmed rabid dogs					
Patients ≤15 years old	53.68	Beta [α- 794; β- 685]	44.00	Beta [α- 264; β- 336]	[2003–2014]
Pr of receiving ERIG in patients ≤15 years of age	98.72	Beta [α- 77; β- 1]	93.33	Beta [α- 14; β- 1]	2014
Pr of receiving ERIG in patients >15 years of age	96.77	Beta [α- 90; β- 3]	100.00	Beta [α- 9; β- 0]	2014
Pr of wound cleaning outside the IPC	14.62	Beta [α- 25; β- 146]	12.50	Beta [α- 3; β-21]	2014 and 2018
Pr of dying of rabies after a four-PEP session	0.00	Beta [α- 0 β- 345]	0.00	Beta [α- 0; β- 123]	[2003–2014]
Pr of dying of rabies after a three-PEP session	0.00	Beta [α- 0; β- 78]	3.03‡	Beta [α- 1; β- 32] ‡	[2003–2014]
Patients bitten by confirmed non-rabid dogs†					
Patients ≤15 years old	54.85	Beta [α- 74,913; β- 61,653]	42.27	Beta [α- 14,865; β- 20,308]	[2003–2014]
Pr of receiving ERIG in patients ≤15 years of age	0.71	Beta [α- 53; β- 7435]	83.84	Beta [α- 358; β- 69]	2014
Pr of receiving ERIG in patients >15 years of age	0.49	Beta [α- 34; β- 6845]	84.64	Beta [α- 226; β- 41]	2014
Pr of wound cleaning outside the IPC	16.91	Beta [α- 2430; β- 11,937]	8.50	Beta [α- 59; β-635]	2014 and 2018
Patients bitten by dogs of unknown status					
Patients ≤15 years old	52.39	Beta [α- 12,567; β-11,422]	50.13	Beta [α- 2852; β- 2838]	[2003–2014]
Pr of receiving ERIG in patients ≤15 years	10.41	Beta [α- 198; β- 1704]	80.00	Beta [α- 156; β- 39]	2014
Pr of receiving ERIG in patients >15 years of age	11.33	Beta [α- 214; β- 1675]	72.97	Beta [α- 108; β- 40]	2014
Pr of wound cleaning outside the IPC	16.54	Beta [α- 627; β- 3164]	7.87	Beta [α- 27; β-316]	2014 and 2018
Pr of dying of rabies after a four-PEP session	0.00	Beta [α- 0; β- 589]	0.00	Beta [α- 0; β- 115]	[2003–2014]
Pr of dying of rabies after a three-PEP session	0.00	Beta [α- 0; β- 104]	0.00	Beta [α- 0; β- 23]	[2003–2014]
Patients bitten by any dog					
Patients ≤15 years old	54.48	Beta [α- 88,274; β- 73,760]	43.37	Beta [α- 17,981; β-23,482]	[2003–2014]
Pr of receiving ERIG in patients ≤15 years	3.46	Beta [α- 328; β- 9140]	82.89	Beta [α- 528; β- 109]	2014
Pr of receiving ERIG in patients >15 years of age	3.81	Beta [α- 338; β- 8523]	80.90	Beta [α- 343; β- 81]	2014
Pr of wound cleaning outside the IPC	16.81	Beta [α- 3082; β- 15,247]	8.39	Beta [α- 89; β- 972]	2014 and 2018
Cost					
Wound cleaning received outside IPC	$5.1	Gamma [shape = 0.67, scale = 7.52]	$5.1	Gamma [shape = 0.67, scale = 7.52]	2018
Transportation	$4.6	Gamma [shape = 0.62, scale = 7.35]	$4.6	Gamma [shape = 0.62, scale = 7.35]	2018
Accommodation	$0.6	Gamma [shape = 0.01, scale = 39.95]	$0.6	Gamma [shape = 0.01, scale = 39.95]	2018
Income loss among adult patients	$3.0	Gamma [shape = 1.38, scale = 2.16]	$3.0	Gamma [shape = 1.38, scale = 2.16]	2018
Income loss among relatives of child patients	$4.7	Gamma [shape = 0.85, scale = 5.6]	$4.7	Gamma [shape = 0.85, scale = 5.6]	2018
Income loss among relatives of adult patients	1.0	Gamma [shape = 0.24, scale = 4.1]	1.0	Gamma [shape = 0.24, scale = 4.1]	2018

* ERIG, equine rabies immunoglobulin; IPC, Institut Pasteur du Cambodge; PEP, post-exposure prophylaxis; Pr, Probability.
† Tested negative or alive at 10 days.

‡ After exclusion due to protocol noncompletion of 2 deaths.

Table 5
Per-patient cost (including indirect costs) in 2018 USD associated with the IPC regimen and the TRC regimen in unvaccinated persons bitten by dogs*.

		IPC regimen		TRC regimen	
		CII bites	CIII bites†	CII bites	CIII bites†
Patients bitten by					
• confirmed rabid dogs	CII bites, p = 0.91% CIII bites, p = 1.45%	$80.3	$81.2	$89.3	$90.1
• confirmed non-rabid dogs‡	CII bites, p = 84.28% CIII bites, p = 84.83%	$43.6	$75.9	$43.6	$75.9
• dogs of unknown status	CII bites, p = 14.80% CIII bites, p = 13.72%	$47.4	$72.0	$56.4	$90.9
Total		$44.5	$75.5	$45.9	$76.8

* p represents the probabilities used in the model.
† Most patients received ERIG.
‡ Tested negative or alive at 10 days.

up in database 2 were deceased. IPC being identified as the expert center for rabies in Cambodia, we can assume that the experts would have been informed of an additional death. We studied the outcomes and costs of patients who did attend facilities and did not have information on patients that did not receive PEP at all. From the data collected at IPC, we cannot know whether the use of the shorter regimen has changed attendance of someone who might not otherwise have sought care. We can, however, hypothesize that the care seeking behavior would not change for the first sessions, as patients did not know upfront how many sessions would be performed. Similarly, since patients paid a flat rate on first attendance, the shorter regimen would not affect initial access.

Finally, our findings pertain to the peculiar environment of IPC and Cambodia, characterized by a high percentage of owned and observable dogs, a high percentage of access to ERIG. We did not address the issue of PEP failure due to direct virus inoculation into the nerve, or human errors in PEP administration.

The clinically- and cost-effective three-sessions IPC regimen is now the first one-week regimen recommended by the World Health Organization [5]. It reduces costs to patients, improves vaccine equity [12] and should receive financial support in GAVI-eligible countries who make the request as part of the current tripartite Zero-by-30 campaign to eliminate canine-mediated human rabies deaths by 2030. However, GAVI halted all rabies vaccine support during the Covid-19 pandemic, which delayed the roll out of the VIS and the alleviation of the financial pressure on patients.

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Ethics approval and consent to participate

All patients had approved the use of their personal data for research purposes and we accessed de-identified patient data. The Cambodian National Ethics Committee for Human Research approved the study (approval #046 dated 20 February 2015).

Availability of data

Data are available upon reasonable request.

CRediT authorship contribution statement

Alicia Le Bras: Conceptualization, Methodology, Software, Visualization, Formal analysis, Writing – original draft. **Kevin Zarca:** Conceptualization, Methodology, Writing – review & editing. **Yiksing Peng:** Data curation, Writing – review & editing. **Malen Chan:** Data curation, Writing – review & editing. **Isabelle Durand-Zaleski:** Conceptualization, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

All authors have nothing to declare.

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Appendix A. Supplementary data

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