Abstract
Thailand is a canine rabies endemic country with an annual prevalence above 1000 reported animals diagnosed rabid [1]. Over 345,000 humans are treated for possible rabies exposures annually [2]. Lack of perception of the disease burden, social, cultural and traditional beliefs play an important role in the failure of canine rabies control. It is unfortunate that health care budgets are increasingly allocated to human post-exposure treatment rather than to the eradication of rabies in the canine animal vector. Children under the age of 15 years represent up to one-half of dog bite victims and of human rabies deaths, but accurate data of dog bite prevalence are not available [3–6]. Large scale pre-exposure immunization of children has been advocated but financial and logistic barriers have hindered implementation. This study analyzes direct medical costs of pre-exposure vaccination (PREP) as a human rabies preventive strategy, against the cost of post-exposure prophylaxis (PEP) in Thai children. Three pre- and post-exposure vaccine regimens are in use and this impacts on cost calculations. It was found that costs of both strategies, PREP of children or PEP of exposed, become equal when the dog bite incidence is 2–30%; depending on which post-exposure treatment regimens (PEP) are used.

Keywords: Rabies; Cost comparison; Pre- and post-exposure vaccination

1. Introduction
Human rabies is largely a disease of poverty, often affecting rural populations in remote regions [7,8]. Canine rabies is mainly a problem for developing countries [7,9]. The annual number of worldwide deaths caused by rabies was estimated at 40,000–70,000 [6] and 30–50% of rabies bite victims and deaths are in children under the age of 15 years [3–6]. An estimated 10 million people worldwide receive expensive, often not optimal, post-exposure rabies prophylaxis (PEP) annually [6,7]. During the past decade, there was a dramatic decrease in rabies deaths in Thailand attributed to improved and more widely available post-exposure treat-
tions) for a previously vaccinated person is considerably less than that of a complete PEP course in a non-immune person. Importantly, scarce and expensive immunoglobulin is not needed in a patient who had PREP [12]. Thailand has been on the forefront of efforts to improve human post-exposure rabies treatment. The Thai Ministry of Public Health reported that a decrease in human rabies deaths during 1990–1998 was inversely related to a triple increase in expensive PEP provided mostly by the public sector [11]. This stimulated us to perform a cost analysis of pre-exposure prophylaxis (PREP) as an alternative strategy and to determine possible savings associated with the most common management schedules for rabies PREP and PEP. Our study focused on children under 15 years as they represent a major risk group for dog bites and rabies.

2. Materials and methods

An analysis model was constructed to compare cost for cohorts of children under 15 years of age who had never received rabies vaccine. The competing strategies were three WHO approved regimens of pre-exposure (PREP) and three regimens of post-exposure rabies prophylaxis (PEP). The cost comparison model was based on four assumptions:

1. The treatment cost for a child bitten by a dog was considered the same whether the animal had been vaccinated or not.
2. The cost of wound care was considered equal in immunized and non-immunized children.
3. The cost was calculated for one episode of dog bite.
4. The cost of any adverse effects from treatment was not included in the analysis.

2.1. Rabies vaccines used in Thailand

Imported purified Vero cell (PVRV, Aventis Pasteur, France) and Purified chick embryo rabies vaccines (PCEC, Chiron, India).

2.2. Pre-exposure (PREP) schedules used in Thailand

PREP 1: One full ampoule of vaccine (PVRV or PCEC) administered intramuscularly (IM) on days 0, 7 and 28. In the hypothetical event of a later exposure, one full dose of vaccine is administered IM on days 0 and 3.

PREP 2: 0.1 mL of 0.5 mL/diluent-containing vaccine (PVRV) administered intradermally (ID) on days 0, 7 and 28. In the hypothetical event of a later exposure, 0.1 mL of vaccine is administered ID on days 0 and 3.

PREP 3: 0.1 mL of 1.0 mL/diluent-containing vaccine (PCEC) administered ID on days 0, 7 and 28. In the hypothetical event of a later exposure, 0.1 mL of vaccine is administered ID on days 0 and 3.

2.3. Post-exposure schedules (PEP) using tissue culture vaccines currently in use in Thailand

PEP 1 (Essen schedule): One full ampoule (PVRV or PCEC) is administered IM on days 0, 3, 7, 14 and 28 with/without immunoglobulin (RIG).

PEP 2 (Thai Red Cross regimen): 0.1 mL of a 0.5 mL diluted vaccine (PVRV) is administered ID at 2 sites on days 0, 3 and 7 followed by 0.1 mL administered ID at one site on days 28 and 90 with/without RIG.

PEP 3 (Thai Red Cross regimen): 0.1 mL of a 1.0 mL diluted vaccine (PCEC) is administered ID at 2 sites on days 0, 3 and 7 followed by 0.1 mL administered ID at 1 site on days 28 and 90 with/without RIG.

2.4. Cost calculations

We started with the option of receiving pre-exposure vaccine or not. Cost of PREP and PEP was estimated using the vaccine and immunoglobulin (RIG) prices currently in place for an outpatient at the Queen Saovabha Memorial Institute (QSMI). This represents the public sector cost. This study considered only direct medical costs including professional services at public sector salaries, vaccine, RIG and medical supplies. However, hypothetical indirect costs such as transportation and loss of wages were also included. Costs were expressed in US Dollars (exchange rate: 1 US$ ∼ 40 Baht).

The mathematical model used was a Monte Carlo simulation technique [29]. One-way sensitivity analysis was performed [29].

Current vaccine and immunoglobulin costs in Thailand are: Imported vaccines (PVRV or PCEC) $8.75 per ampoule (Human diploid cell rabies vaccine is available in the private sector but rarely used and not included in this study). Locally made equine rabies immune globulin (ERIG) $33.75 per 5 mL vial. Human rabies immune globulin (HRIG) $37.5 and $75.00 for the local or the imported products.

2.5. Cost of PREP with PEP boosters (No immunoglobulin required)

The lowest price for each option is that in the public sector. The range represents the difference between public sector cost and that paid by patients in the private health care sector.

PREP 1. The cost for the three full vials injected intramuscularly is $18.75–34.50. The additional cost of later receiving two rabies post-exposure boosters would be $32.25–39.50.

PREP 2. The cost of the Thai Red Cross intradermal regimen using 0.5 mL/vial of PVRV vaccine is $4.00–7.25. The additional cost of two rabies post-exposure boosters is $19.75–23.50.

PREP 3. The cost of the Thai Red Cross intradermal regimen using 1.0 mL/ampoule of PCEC vaccine is $2.00–3.75.
The additional cost of two rabies post-exposure boosters is $18.00–21.75.

2.6. Cost of PEP without prior PREP

**PEP 1.** The cost of five full vials of 0.5 mL/vial or 1.0 mL/ampoule vaccine IM is $64.50–74.50.

**PEP 2.** The cost of Thai Red Cross ID regimen using 0.5 mL/vial of PVRV vaccine is $33.00–47.25.

**PEP 3.** The cost of Thai Red Cross ID regimen using 1.0 mL/ampoule of PCEC is $28.75–37.25.

In severely rabies exposed patients (WHO category III) ERIG or HRIG is also required [12]. The cost is US$ 27.50 or US$ 75.00, respectively (in the public sector and up to double in the private sector). This must be added to the primary cost of the PEP regimens 1–3. PREP would be given at schools without added transportation costs or loss of parental wages. PEP, on the other hand, requires transportation to a medical center and presence of parents. Estimates for such costs have been included in the analysis.

3. Cost analysis

Based on a Monte Carlo simulation, a technique that will approximately describe the population by using repeated sampling [29], the pre-exposure vaccination cost would be $18.75–34.50, $4.00–7.25 and $2.00–3.75 per child for PREP regimen 1, 2 and 3, respectively. Total costs for one rabies-exposed child are $51.00–74.00, $23.75–30.75 and $20.00–25.50 for PREP regimen 1, 2 and 3, respectively. If a child has not received PREP, costs per child were the least in PEP regimen 3 (using the Thai Red Cross intradermal regimen and 1.0 mL diluted vaccine without RIG) $28.75–37.25. The highest cost of $135.50–154.00 occurred in PEP regimen 1 (The schedule with five full IM doses with HRIG. This schedule is rarely, if ever, used in the Thai public sector).

4. Sensitivity analysis

To determine at what point the cost of PREP is equal to PEP, we used a sensitivity analysis [29]. We then found that equal cost of PREP with PEP depended on the prevalence of dog bites and the regimen used for PEP (PEP 1-3) and whether ERIG or HRIG was utilized. An equal cost of the intramuscular full dose PREP (PREP 1) regimen with the intramuscular PEP 1 and HRIG was reached at a dog bite prevalence of 25%. In case of the intramuscular PREP 3 (without RIG), equal cost would occur at a dog bite prevalence of only 2% when compared to the intramuscular PEP 1 with HRIG (see Table 1). However, HRIG is costly and in short supply and virtually never used by the Thai public sector except for the Thai Red Cross Society which manufactures a limited supply. Intradermal PREP 3, compared to PEP 3 with ERIG is a more realistic model that would result in equal cost for PREP and PEP at a dog bite prevalence of 7%.

5. Discussion

The dog is the responsible vector for approximately 95% of human rabies cases in Asia [7,9,13,23,24,30]. We suggest that elimination of dog rabies is less expensive than increased efforts to provide effective post-exposure treatment or initiating universal pre-exposure vaccination of children [30–32]. Canine rabies control thus remains the only long-term cost-effective means of eliminating this disease [7,10,31]. In countries like Thailand, which have a huge stray or community dog population, such a goal could only be achieved in conjunction with sustainable and humane dog population control and regular dog vaccination where at least 75% of canines are kept immunized [9,10,23]. Cultural and religious barriers, as well as lack of motivation and funding, have prevented implementing this in Thailand, the Philippines, Indonesia and India. There is also lack of public awareness of the social and financial burden imposed by this disease which impacts largely on

### Table 1

Cost equivalence expressed as percentage of dog bite prevalence

<table>
<thead>
<tr>
<th>Post-exposure regimens</th>
<th>PREP 1 (%)</th>
<th>PREP 2 (Vaccine 0.5 mL/vial) (%)</th>
<th>PREP 3 (Vaccine 1.0 mL/ampoule) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEPR 1: full dose IM</td>
<td>0</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>PEPR 1 and ERIG</td>
<td>0</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>PEPR 2: ID 2-2-2-0-1-1 (vaccine 0.5 mL/vial)</td>
<td>0</td>
<td>30</td>
<td>14</td>
</tr>
<tr>
<td>PEPR 2 and ERIG</td>
<td>0</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>PEPR 2 and HRIG</td>
<td>0</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>PEPR 3: ID 2-2-2-0-1-1 (vaccine 1.0 mL/ampoule)</td>
<td>0</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td>PEPR 3 and ERIG</td>
<td>0</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>PEPR 3 and HRIG</td>
<td>0</td>
<td>14</td>
<td>7</td>
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</tbody>
</table>

* Cost equivalence expressed as percentage of dog bite prevalence. Cost for PREP of 100 children plus cost for a later PEP of 2 out of 100 PREP children is equal to cost for PEP of 2 non-immunized children. If prevalence is less than s, PEP will become lesser in cost. On the contrary, if the prevalence is higher than s, PREP will become lesser in cost.

* PREP, no immunoglobulins required.

* Equal cost did not occur.
the lower socio-economic strata of society [7]. Demand for post-exposure treatment in Thailand increased by 10–15% each year [10] and is unlikely to reduce exposures of humans to rabies. Recently, there has been some advocacy of wide-scale pre-exposure vaccination of high-risk populations. It has the advantage of making any post-exposure treatment of a pre-vaccinated individual much less expensive. Only two booster injections would be required and no costly and scarce immunoglobulin is needed if such a person is later exposed [12].

However, including rabies pre-exposure vaccination in an expanded program of immunization (EPI) for children would require a high annual budget. Such a program might be more applicable if it is limited to endemic regions with a high prevalence of dog bites and high rabies risk, and then only as a temporary measure till canine control is activated. Several assumptions were made for our study and only direct treatment costs were included. Relevant indirect social costs related to PEP, other than travel and wages lost, were not included. Cost comparison between pre-exposure and post-exposure vaccination in target groups showed that equal cost occurred when the dog bite incidence is 7–14%, using the most commonly applied PREP and PEP schedules in Thailand. If rabies in the animal vectors is not eliminated, expenses related to prevention of the disease in both humans and animals are likely to increase further [6,10,13]. In the south and southeast Asian region alone, an estimated 1.5 million post-exposure treatments were administered at an estimated cost of 25 million US dollars annually [13].

6. Conclusion

The cost for post-exposure treatment of a severely exposed child ranges from $28.75 to $125.00. Pre-exposure immunization is only $2.00–7.25 with an additional cost of $18.00–23.50 if post-exposure booster vaccination is later required. The lower costs were estimated by using the WHO approved reduced dose intradermal vaccine schedule. Budgetary limitations in developing rabies endemic countries must consider health care costs as well as best care protocols. We have shown that pre-exposure vaccination has a cost scale which increases with dog bite prevalence. When using the least expensive vaccination schedule and no immunoglobulin, pre-exposure vaccination (PREP) is cost-comparable with post-exposure prophylaxis (PEP) when the probability of a dog bite is approximately 25%. If ERIG is used, cost-comparability occurred at 7% dog bite prevalence. The lowest cost-comparability occurred in the group where HRIG is used (at 3% dog bite prevalence) but this schedule is virtually never used in Thailand. If vaccine cost can be significantly reduced, as seen when one uses the 1.0 mL rather than 0.5 mL diluted product, cost-comparability will occur at a lower dog bite prevalence (down from 12 to 7% for ERIG and from 6 to 3% for HRIG). It should, however, be noted that potency of a vaccine dose is important when providing PEP for this invariably fatal disease [33]. WHO recommended that all tissue culture rabies vaccines have a potency greater than 2.5 IU/mL. This concept was agreed on and published before reduced dose intradermal post-exposure (PEP) regimens had been developed [9]. Current ampoules of PVRV and PCEC imported and used in Thailand have potencies above 6.0 IU per 0.5 or 1.0 diluent containing ampicillin. In regions where rabies control measures in dogs are not effective and there is a high incidence of canine rabies, systematic pre-exposure vaccination of children might be considered as a temporary strategy. It must never detract from efforts to control rabies in the canine vector. In conclusion, we can say that the intradermal PREP 2 or PREP 3 method combined with PEP 2 or PEP 3, with ERIG, are the most likely and cost-benefit effective schedules to be used in Thailand. Cost of PREP and PEP would then meet at a dog bite prevalence of 12 and 7%. Unfortunately, we could not find any reliable data for the current dog bite prevalence in Thailand. However, we do know that over 30% of Thai children have experienced a dog bite by the age of 15 [3,4]. Assuming that bites are unlikely in the first 2 years of life, we calculated a prevalence of approximately 2.3 bites per year for central Thailand.

Acknowledgement

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References


