THE ASSOCIATED FACTORS NON-COMPLIANCE OF RABIES POST EXPOSURE VACCINATION AMONG DOG BITES PATIENTS IN PERLIS

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by

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LIST OF ABBREVIATION

Adj. OR	Adjusted Odd Ratio
CI	Confidence Interval
CPRC	Crisis Preparedness and Response Center
DALY	Disability Adjusted Life Years
FAO	Food and Agriculture Organization of the United Nations
GARC	Global Alliance for Rabies Control
IQR	Interquartile Range
MOH	Ministry of Health, Malaysia
OIE	World Organisation for Animal Health
OR	Odd Ratio
PEP	Post-Exposure Prophylaxis
PEV	Post Exposure Vaccination
RABV	Rabies Virus
RIG	Rabies Immunoglobulin
USD	United States Dollar
VNA	Virus-Neutralising Antibodies
WHO	World Health Organization

LIST OF SYMBOLS

$\chi 2$	Chi-Square Value
<	Less Than
α	Alpha
=	Equal
%	Percentage
km^2	Kilometre Square

ABSTRAK

FAKTOR-FAKTOR BERHUBUNG KAIT KETIDAKPATUHAN VAKSINASI PASCA PENDEDAHAN RABIES DIKALANGAN PESAKIT GIGITAN ANJING DI PERLIS

Latar belakang: Ribuan orang meninggal dunia disebabkan oleh penyakit Rabies anjing - perantara, dan kerugian ekonomi berbilion USD juga dilaporkan. Vaksinasi Pasca Pendedahan Rabies merupakan pencegahan Rabies di kalangan manusia yang paling penting dan paling berkesan sekiranya diberikan tepat pada masanya dan sesuai dengan garispanduan. Ketidakpatuhan siri vaksinasi dilaporkan terutama disebabkan oleh kos yang perlu ditanggung untuk vaksin, sedangkan perkara itu tidak sepatutnya berlaku di Malaysia. Wabak rabies pada anjing baru-baru ini di Perlis menghapuskan status negara bebas Rabies. Oleh itu, adalah amat mustahak untuk mengenal pasti faktor-faktor berhubung kait dengan ketidakpatuhan terhadap Vaksinasi Pasca Pendedahan Rabies di Perlis dalam mencapai sifar kematian penyakit Rabies anjing - perantara menjelang tahun 2030.

Objektif: Untuk menentukan kadar dan faktor - faktor berhubung kait dengan ketidakpatuhan Vaksinasi Pasca Pendedahan Rabies di kalangan pesakit gigitan anjing antara tahun 2015 - 2020 di Perlis.

Metodologi: Ini adalah kajian kohort retrospektif dengan menggunakan registri Kes Gigitan Haiwan Berpontensi Rabies Perlis. Pesakit gigitan anjing yang berdaftar antara bulan Julai 2015 hingga Jun 2020 dijadikan sebagai sampel. Analisis deskriptif digunakan untuk menggambarkan sosiodemografi manakala analisis regresi logistik

digunakan untuk menentukan faktor berhubung kait dengan ketidakpatuhan terhadap Vaksinasi Pasca Pendedahan Rabies. Pesakit yang menghentikan penerimaan vaksinasi pada bila-bila masa dalam tempoh yang ditetapkan tanpa mempunyai alasan perubatan digunakan sebagai definisi kepada ketidakpatuhan vaksinasi.

Keputusan: Peratusan ketidakpatuhan Vaksinasi Pasca Pendedahan Rabies di Perlis pada Julai 2015 hingga Jun 2020 adalah 19.5% (95% selang keyakinan (CI): 16.1, 23.0) berdasarkan kepada analisis ke atas 507 data pesakit yang memenuhi kreteria pimilihan. Analisis regresi logistik berganda menunjukan bahawa etnik Siam mempunyai dua kali lebih ganda cenderung untuk menjadi tidak patuh (Nisbah ganjil terlaras (Adj. OR): 2.00, 95% CI: 1.06,3.76, p-value = 0.031) dan digigit anjing pada tahun ketiga wabak (Adj. OR: 0.27, 95% CI: 0.12,0.59, p-value = 0.001), tahun keempat wabak (Adj. OR: 0.24, 95% CI: 0.11,0.52, p-value < 0.001) serta tahun wabak kelima wabak (Adj. OR: 0.20, 95% CI: 0.09,0.44, p-value <0.001) mempunyai kemungkinan lebih rendah untuk ketidakpatuhan.

Kesimpulan: Walaupun vaksin Rabies di Malaysia adalah sentiasa tersedia dengan mudah dan tanpa bayaran pada setiap masa, terdapat sebahagian (19.5%) di negeri Perlis tidak patuh dengan vaksin ini sehingga medatangkan risiko yang lebih tinggi untuk menghidap penyakit Rabies. Etnik Siam dan individu yang digigit anjing dalam tempoh permulaan wabak mempunyai kecenderungan lebih tinggi menerima vaksin ini dengan tidak lengkap.

KATA KUNCI: Rabies, Vaksinasi, Ketidakpatuhan, Gigitan Anjing, Profilaksis Pasca Pendedahan

ABSTRACT

THE ASSOCIATED FACTORS NON-COMPLIANCE OF RABIES POST EXPOSURE VACCINATION AMONG DOG BITES PATIENTS IN PERLIS

Background: Thousands of people succumbed to dog-mediated human Rabies, and billions of USD economic lost have been reported. Rabies Post Exposure Vaccination (RPEV) remains the most fundamental and effective prevention of human Rabies if administered in a timely and appropriate manner. Non-compliance of the vaccination series is mainly reported because of the cost incurred for the vaccine, but that shall not happen in Malaysia. The recent canine Rabies outbreak in Perlis takes away the status of the free-Rabies country. Thus, it is vital to identify the factors associated with the non-compliance towards RPEV in Perlis in achieving zero dog-mediated human Rabies death by 2030.

Objectives: To determine the proportion and associated factors for non-compliance of RPEV among dog bite patients between 2015 - 2020 in Perlis.

Methodology: This is a retrospective cohort study using Perlis Rabid Potential Animal Bite Registry. Dog bite patients registered between July 2015 to June 2020 were selected for the sample. Descriptive analyses utilised to describe the sociodemographic while logistic regression used to determine the factor associated with non-compliance of RPEV. Non-compliance of RPEV define as the dog bite patient who discontinued the vaccination at any point during the recommended course without a medical reason.

Results: The proportion of non-compliance for RPEV in Perlis from July 2015 till June 2020 was 19.5% (95% confidence interval (CI): 16.1,23.0) based on the analysis on 507 dog bite patient's data that fulfil the criteria for sample selection. Multiple logistic regression analysis shown that Siamese has significantly two-times (Adjusted Odd Ratio (Adj. OR): 2.00; 95% CI: 1.06,3.76; p-value = 0.031) odd higher to become non-compliance and being bitten during 3rd (Adj. OR: 0.27; 95% CI: 0.12,0.59; p-value = 0.001), 4th (Adj. OR: 0.24; 95% CI: 0.11,0.52; p-value < 0.001) and 5th (Adj. OR: 0.20; 95% CI: 0.09,0.44, p-value < 0.001) year of the outbreak has significantly lower odds to non-comply with RPEV.

Conclusions: Despite the vaccine were available, accessible, and affordable most of the time to obtain in Malaysia, and there was still a portion (19.5%) in Perlis that did not comply with the RPEV series leads to a higher risk to develop human Rabies. Siamese ethnicities and dog bite patients who bitten at the beginning of outbreaks were more likely to receive incomplete RPEV.

KEYWORD: Rabies, Vaccination, Non-Compliance, Dog Bite, Post Exposure Prophylaxis

CHAPTER 1

INTRODUCTION

1.1 Background

Dog bites accounted for millions of injuries annually and contributed to the higher mortality rate in low- and middle-income countries (Hampson *et al.*, 2015; World Health Organization (WHO), 2018a). Rabies is one of the zoonosis diseases where it is also well-known for its fatality in human once obvious clinical manifestation excretes as a result of the dog bite (Fooks and Jackson, 2020). Primary human Rabies prevention remains the mainstream to curb the disease, including public education, mass dog vaccination, human vaccination, and Post Exposure Prophylaxis (PEP) due to the limited success of current treatment (Fooks and Jackson, 2020; Miranda and Miranda, 2020). A series of Rabies PEVs were administered in a timely and appropriate manner has a very potent effect of preventing the disease and escaping this deadliest zoonotic disease (WHO, 2018b).

In spite of the fact that Rabies has known to happen in Malaysia since 1845, and the data of its incidence are only available since 1924, Malaysia still has problems maintaining as Rabies free country (Ganesan and Sinniah, 1993). Recently, Malaysia has been reported of 34 cases of human Rabies which 32 of the patients pass away (N. H. Abdullah, 2021). Despite the Rabies vaccination is one of the potent prevention of human Rabies, lack of compliance towards Rabies PEV has been established as one of the main culprits to contract human Rabies then abolish the known Rabies free country (Ghosh *et al.*, 2020; Guo *et al.*, 2018). We are exploring the factor associated with lack of compliance, given an insight into the targeted prevention strategy to optimise the Rabies PEV compliance in the future.

1.2 Statement of Problem

Despite having a very potent vaccination, Hampson *et al.* (2015) estimate canine Rabies causing almost 59000 (95% Confidence Interval [CI], 25000,159200) human Rabies death annually worldwide, with Asia and Africa continents are the significant contributors to this estimation. Besides that, globally, overall economic costs of approximately 8.6 billion United States dollars (USD) and 3.7 million Disability Adjusted Life Years (DALY) losses were reported. WHO has joined forces with the World Organisation for Animal Health (OIE), the Food and Agriculture Organization of the United Nations (FAO), and the Global Alliance for Rabies Control (GARC) as United Against Rabies collaboration develop a framework to eliminate dog-mediated human Rabies with the vision of zero human death from the dog-mediated Rabies by 2030 (GARC, 2015; WHO *et al.*, 2018). One of the strategies in the global strategic plan to eliminate dog-mediated Rabies by 2030 is effectively using vaccines and technologies by ensuring equitable, affordable, and timely access to health care, medicines, and vaccines (WHO *et al.*, 2018). Nonetheless, the non-compliance rate of Rabies PEV widely ranges between countries in the world, ranging from 22.0% to 55.6% (Diallo *et al.*, 2019; Romero-sengson, 2013; Tenzin *et al.*, 2011; Tran *et al.*, 2018, 2019; Vinay *et al.*, 2013).

Malaysia was free from Rabies after last reported human cases in 1998 and canine Rabies in 1999, which later being accredited Rabies Free in July 2013. However, Malaysia lost its free status due to a recent outbreak in the Northern states of Malaysia in 2015 (Navanithakumar *et al.*, 2019). Bamaiyi (2015) reported that during the 2015 Canine Rabies outbreak in Malaysia, Perlis has the most significant number of canine Rabies cases compared to Kedah and Pulau Pinang.

1.3 Rationale

Previous studies conducted in this area reveal that the most significant obstacle for discontinuation of PEP is the cost incurred for the vaccine (Diallo *et al.*, 2019; Romero-sengson, 2013; M. B. Sambo, 2012). However, the Rabies Post Exposure Vaccination (PEV) is provided free of charge at any government healthcare facility in Malaysia. There was very limited study worldwide in such a setting, especially in Malaysia. As a result, it is essential to recognise the potential associated factors pertaining to the incomplete series of the Rabies PEV in a very low to free cost setting.

The challenges never end on the road towards eliminating dog-mediated Human Rabies globally or in Malaysia. Recognising the associated factor with the non-compliance of the Rabies vaccination opens up an excellent opportunity for a new effective health education and vaccination services delivery. Ultimately, the prevention and control of human Rabies is at optimum and reduces the morbidity and mortality of the human Rabies.

Even so, up to date, there was no published study yet in Malaysia regarding Rabies PEP or Rabies PEV. Although there are numerous studies on this similar issue, socio-cultural belief background and Rabies vaccination delivery program in Malaysia is totally different from the previous study in the literature. Our study highlighted several factors that never being explored in other settings before in the previous literature on the similar issue. Thus, the finding of this study intended to assist Perlis State Health Department as the stakeholders to prioritise strategy to enhance the compliance rate with the ultimate goals of zero dog-mediated Rabies death by 2030.

1.4 Research Questions

1. What is the proportion of non-compliance of Rabies PEV among dog bite patients between 2015 to 2020 in Perlis?
2. What factors are associated with non-compliance of Rabies PEV among dog bite patients between 2015 to 2020 in Perlis?

1.5 Objectives

1.5.1 General Objective

To determine the proportion and its associated factors for non-compliance of Rabies PEV among dog bite patients between 2015 - 2020 in Perlis

1.5.2 Specific Objectives

1. To determine the proportion of non-compliance of Rabies PEV among dog bite patients between 2015 - 2020 in Perlis
2. To determine the associated factors for non-compliance of Rabies PEV among dog bite patients between 2015 - 2020 in Perlis

1.6 Research Hypotheses

There is an association between sociodemographic factor, animal factor, exposure factor, and treatment factor with non-compliance of Rabies PEV.

CHAPTER 2

LITERATURE REVIEW

The literature search was conducted by using multiple search engines available freely in the web, includes PubMed and Google Scholar. Besides that, the university subscribed database also being utilised as a medium to look for literature includes Science Direct and Wiley Online Library. Numerous searching strategy was applied, such as a combination of terms with the use of Boolean operators (AND, OR, NOT). List of keywords applied during search Rabies, Rabies Post Exposure Vaccination, Rabies Post Exposure Prophylaxis, Non-Compliance, Compliance, Completion and Adherence, Medical Non-compliance, Theory of Non-Compliance.

2.1 Epidemiology of the Rabies

Rabies has eliminated from the dog population in most industrialised countries. However, most developing countries are still struggling to control and end the Rabies' endemicity neither in human nor in the dog (Fooks and Jackson, 2020). Globally, there was an estimated 59 000 (95% CI: 25000, 159000) people succumb to the Rabies annually, leading to known of the deadliest of all zoonotic diseases. The majority of the death (98%) resulted from infections with the Rabies Virus (RABV) transmitted from dog bites (Fooks and Jackson, 2020; Hampson *et al.*, 2015). Asia, including the Indian subcontinent (59.6%) and Africa (36.4%), account for more than half of the human Rabies death annually. As the single most human Rabies death, India accounted for 35% of global estimation. However, the poorest countries in sub-Saharan Africa estimated to be the highest estimated per-person death rate (Hampson *et al.*, 2015). Figure 2.1 illustrates the global distribution of human Rabies death.

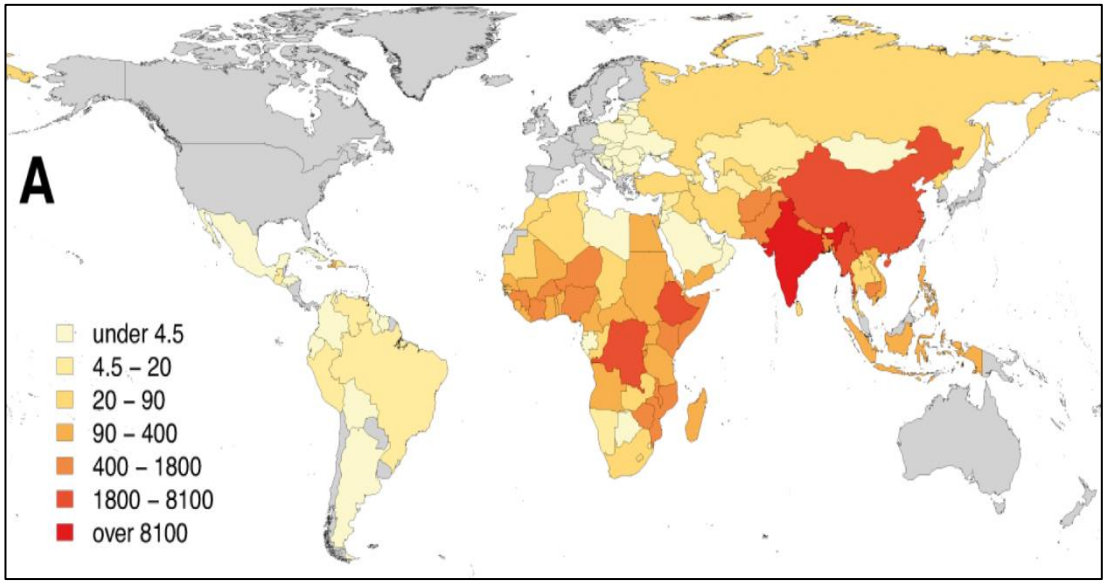

Figure 2.1: The distribution of estimated human deaths worldwide due to rabies. Adopt from *Estimating the Global Burden of Endemic Canine Rabies (Hampson et al., 2015)*

Western Pacific Region has not been achieved Rabies elimination status yet due to the endemicity of the Human Rabies in China, the Philippines, and Vietnam. Malaysia recognised as one of the countries in the Western Pacific Region that achieved Rabies-free status up to the recent outbreak of human and canine Rabies in 2015 (WHO, 2019). Malaysia documented the first case of Rabies among dogs in 1925 in Perlis, neighbouring Thailand, where a high prevalence of Rabies reported (Navanithakumar *et al.*, 2019). Sundry of the significant outbreak occurred in 1945 in Province Wellesly (known as Seberang Perai nowadays) and Perak subsequently in 1952 in Selangor 1952 (Ganesan and Sinniah, 1993). Latest, an outbreak in Sarawak among humans has been reported since 1 July 2017 involving 34 cases of human Rabies whom 32 of them succumbed to the disease. The remaining two who survive ends with severe neurological sequelae (N. H. Abdullah, 2021).

2.2 Clinical-Pathophysiology of Dog Bites and Rabies

The causative agents of Rabies belong taxonomically to the genus of *Lyssavirus* and the family of *Rhabdoviridae*. All mammals are susceptible to RABV infection due to the conservation of cell receptors and structural features associated with the central nervous system (Jackson, 2018; Marston *et al.*, 2018; Zhang *et al.*, 2008). A broad range of mammalian species primarily within the *Carnivora*, such as fox, skunk, coyote, raccoon order, serves as reservoir hosts of RABV worldwide. On the other hand, *Chiroptera* or bats are only primary hosts of RABV in the New World, complicating disease elimination strategies in terrestrial animals in the Americas. However, domestic dogs (*Canis lupus familiaris*) remain the main vital hazard worldwide as it is nearly 99% causing human Rabies death and by far pose the greatest threat to public health (Gilbert A., 2018; WHO, 2018).

The transmission transpired once infected saliva of the host transmits into a healthy person through a majority of it by a rabid animal bite. Other modes of virus transmission are extremely rare via ingestion of infected animals or contamination of the oral mucosa (Fooks and Jackson, 2020). Ironically, humans do not typically spread Rabies in a human-to-human manner as humans are a dead-end host of Rabies. According to Lu *et al.* (2018), tissue or organ transplantation is the most frequent way to transmit the RABV from one human to another, which laboratory results have confirmed. In history, several countries in the world, United States, Germany, Kuwait and China, reported an outbreak of human Rabies resulting from a vascular tissue and solid organ transplant from a single infected donor. There were sundry reports on the human-to-transmission previously, but the exact transmission route unable to establish and some of the proposed transmission had not been reporting anymore (Fooks and Jackson, 2020).

The incubation period varies from few days to several years; most apparently, it appears between 20 to 90 days in humans but maybe as long as in years and as short as in few days after exposure. Shankar *et al.* (2012) reported a probable 25 years incubation period in Goa, India. A study in China reveals the median incubation period varied by exposure and age group as follow (1) median incubation period for category II is 80 days (IQR 37-222) while category III exposure is 61 days (IQR 31-138), (2) bites on the head, face, neck, and hands are 58 days (IQR 30-115) while bite on the other part of the body is 76 days (IQR 37-218), (3) children aged below 15 years old in 52 days (IQR 25-127) is the shortest as compare with other age groups (Guo et al., 2018).

The pathogenesis of human Rabies begins with the inoculation of the virus. RABV binds to the nicotinic acetylcholine receptor on the postsynaptic membrane of the neuromuscular junction in the muscles near the injury site, enabling it to cross the synapse. The RABV travel to the spinal cord or cranial motor ganglia in the brainstem via motor neurons by retrograde fast axonal transport. Once the virus reaches the brain, it is causing neuronal dysfunction rather than structural degeneration, as demonstrating in many animal studies (Fooks and Jackson, 2020; Jackson, 2018).

The phenomenon is the turning point where the subclinical stage converted into the clinical stage in the natural history of disease whereby the neuronal dysfunction in the brains results in Rabies' prodromal symptoms. Ultimately, the RABV has undergone centrifugal spread salivary glands, cornea, skins, and other organs (Fooks and Jackson, 2020; Jackson, 2018).

2.3 Management of Dog Bite in Malaysia

Malaysia launched its interim guideline for Human Rabies prevention and control in Malaysia back in 2015 after detecting Canine Rabies in Perlis. The management of dog bites includes clinical case management and Rabies' public health control, as outlined in **Figure 2.2** (Ministry of Health, Malaysia (MOH), 2015).

The notification required for Human Rabies exposure, which further classified with definition as follow: possible exposure (a person who had close contact, in the way of bites or scratch, with an animal displaying clinical signs consistent with Rabies at the time of the exposure, or within ten days following exposure in the rabies-infected area) and exposed (a person who has had close contact, in the way of bites or scratch, with a laboratory-confirmed rabid animal). All notified cases shall notify within 24 hours and being investigated by the district health office immediately. The investigation findings will also share with the veterinary district office to obtain the dog status (has Rabies risk or no Rabies risk) within 48 hours (MOH, 2015).

All the notification, investigation findings, and information on the cases will be then reported to the state health department and finally end up to the Headquarters of the MOH in Putrajaya (MOH, 2015). Clinical case management of the dog bite would depend on the location of the bites, the patient's overall health status, and the Rabies vaccination status of the dog. Generally, the initial clinical management of dog bites takes place in the general practice, whether in the primary health clinic, private general practitioners, or emergency department in the hospital. The Malaysia interim guideline is incoherent with the WHO recommended clinical case management through immediate commencement of Rabies PEP (MOH, 2015; WHO, 2018b).

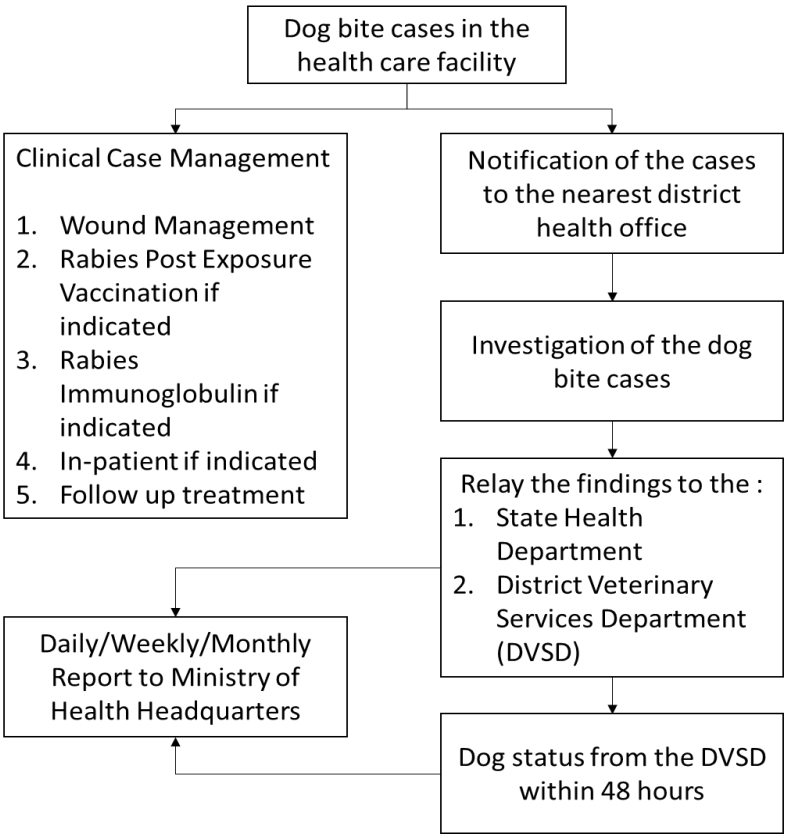

Figure 2.2: Flowchart for the management of dog bites cases in Malaysia. Adopt from *Interim Guideline for Human Rabies Prevention & Control in Malaysia* (MOH, 2015)

2.4 Rabies PEP

WHO recommended every exposure to a rabid potential animal, especially a dog, to practice Rabies PEP. The first step is, as soon as possible, for the wound ought to wash thoroughly and to flush the wound with a copious quantity of water for at least 15 minutes. It is recommended by WHO to use soap during the wash, and native remedies are firmly discouraged to avoid secondary wound infections (WHO, 2018b). In a study by M. Sambo *et al.* (2014), almost 95% of the respondents did not seem aware that wound washing with soap before attending any healthcare facility is the earliest management for preventing human Rabies. The situation explained as the leading source of information for the knowledge of Rabies is their contact such as parents, neighbours, and friends.

The vaccination in the PEP component targets individuals who encounter exposure and sustain injury classified as category II and III exposure. WHO recommended several regimes involving administration via intramuscularly (two-weeks or three-week regime) or intradermally (two-sides, four-sides, or simplified four-sides regime) as summarised in the Table 2.1 (WHO, 2018b). Globally, the standard practice based on the decision of the country where the regime approve by WHO or Advisory Committee on Immunization Practices, Unites States of America (Hampson *et al.*, 2011)

Table 2.1: Summary of the approved Rabies PEV administration regime.

Name of the regime	Day of injection	No. of injection per visit	Doses of vaccine per injections (ml)	Route of administration
Essen 5-dose	0, 3, 7, 14	1, 1, 1, 1, 1	1.0	Intramuscular
Zagreb	0, 7, 21	2, 1, 1	1.0	Intramuscular
Essen 4-dose	0, 3, 7, 14	1, 1, 1, 1	1.0	Intramuscular
Updated Thai Red Cross	0, 3, 7, 28	2, 2, 2, 2	0.1	Intradermal

Source: *Evaluation of cost-effective strategies for rabies post-exposure vaccination in low-income countries (Hampson et al., 2011)*

In Malaysia, all healthcare facilities utilised Essen 4-dose regime as the standard practice. This regime involved a series of single injections intramuscularly on Day zero (date of first vaccine administered), Day Three, Day Seven, and finally on Day 14. However, there is a slight difference between states in Malaysia where there are no Rabies cases. The commencement of vaccination depends on the assessment by infectious diseases physicians in the hospital (MOH, 2015).

Active immunisation through vaccination stimulates the host immune system, and, as a result, virus-neutralising antibodies (VNA) produced approximately seven to 10 days after initiation of vaccination. By approximately Day 14–28 (after administering fourth vaccine doses), VNAs at the summit. The virus can invade host neurons, spreads to the central nervous system (CNS), and causing the disease, with an inevitably fatal consequence in the absence of early and adequate PEP (Rupprecht *et al.*, 2010). Rabies post-exposure vaccination is very potent and very effective in forestall human Rabies if administered appropriately and timely (Guo *et al.*, 2018; Rupprecht *et al.*, 2010).

The last feature of PEP is the administration of passive immunisation known as Rabies Immunoglobulin (RIG) at the site of bite injury as recommended by WHO for those who encounter category three of exposure (WHO, 2018b). As for Malaysia, due to the global shortage, the decision for RIG administration is based on the individual assessment by the Infectious Disease physician. It highly recommends being given together with the first dose of Rabies vaccine and yet can delay up to seven days post-exposure (MOH, 2015; WHO, 2018b).

The route of administration of this immunoglobulin shall infiltrate around the wound at a total dose. However, it should be given via intramuscular distantly from the vaccine injection sites if there was remaining (MOH, 2015). Hence, whenever the RABV is available in tissue at the entry site of the body, it can be neutralised by the passive immunisation of RIG (Rupprecht *et al.*, 2010). The RIG availability in Malaysia is limited and procure at several state hospitals spreading out accordingly to the management zone due to high cost and short expiry date. Howbeit, it is not an issue to mobilise the RIG whenever required as the stock regularly monitors at the national level in a short time (MOH, 2015).

2.5 The concept of medical non-compliance

The medical compliance of medical prescribes pharmacological and non-pharmacological management is an area of interest for researchers over the past decade. However, defining the term compliance itself is not a clear agenda as it ends up without a consensual definition. Besides, there are various terms interchangeable used in the literature to describe "compliance" as "adherence" and "concordance," but the difference in terms of the definition is poorly understood (Kleinsinger, 2003; Rafii *et al.*, 2014). After all, the consequences for non-compliance are well established in the literature, which elevated the risk of contracting the disease, increasing hospitalisation rate, growing up the financial burden for healthcare, and wasting the effect of the unoptimised dose of medication (Rafii *et al.*, 2014).

Kleinsinger (2003) defining the non-compliance behaviour based on four criteria: (1) the medical illness is potentially life-or-death and has a markedly dwelling the quality and length of life; (2) there are at least a single clinical management exist in such a way that significantly take the edge off the risk contracting the complication; (3) accessibility towards the treatments is not an issue; and lastly (4) the patient considerably departs from the normality of other patients in term of compliance with follow up, management plan or medical advice. The criteria by Kleinsinger fit well with the Rabies PEV as the previous literature illustrate the tremendous potential and effectiveness as primary prevention for human Rabies (Guo *et al.*, 2018; Rupprecht *et al.*, 2010). Rabies PEV in Malaysia is unarguable as the services available at the government hospital at all the time at almost free-of-charge (MOH, 2015).

The health belief model was one of the earliest models developed to understand the heart of the non-compliance problem following free Tuberculosis screening program failure and evolve a few years later to explain the behaviour in response to medical illness, especially medical regimes. The model provides a theoretical explanation of non-compliance behaviour, as summarised in **Table 2.2** (Onoruoiza *et al.*, 2015; Ross and Guggenheim, 1983).

Table 2.2: The critical component, definition, and explanation of Health Belief Models

Key Component	Definition	Explanation
Perceived susceptibility	Beliefs about risk contracting the health problem	The models propose that individuals with low perceived susceptibility are more eagerly encountering risky behaviour, including non-compliance.
Perceived severity	Belief about the potential severity and its consequences	The models propose that individuals with high perceived severity more likely to prevent the disease, for instance, comply with the medical treatment.
Perceived Benefits	Belief about the value of the action which reduces the severity or seriousness of the disease	The models propose that individual who believes the recommended medical treatment would have the advantage if compliance achieved.
Perceived Barriers	Belief about the hurdles towards the action	The models propose that individuals have outweighed the benefit rather than the barrier, such as expense and inconvenience for action.
Cue for action	A trigger mechanism or cause for the behaviour to take place	The trigger mechanism such as public service announcement act as a catalyst for the changes in behaviour
Self-efficacy	Competence to act or change the behaviour	It added that once the model expands to apply on the long-term behaviour changes such as diet modification and exercise

Sources: Using Health Beliefs Model as an Intervention to Non Compliance with Hypertension Information among Hypertensive Patient and Health education: theoretical concepts, effective strategies and core competencies (Onoruoiza *et al.*, 2015; WHO, 2012)

A study among travellers acknowledged that having heard of Rabies and the activity risk to contract rabies not necessarily will be perceived risk leads as the cardinal reason for not getting vaccinated (Marano *et al.*, 2019).

2.6 Compliance towards Rabies PEP

Non-compliance rate worldwide spread out in a great range depends on assorted factors. Most of the compliance rate or the other ends rate derives from the hospital-based or medical registry-based data in a single centre or multi-centre state or national level (Diallo *et al.*, 2019; Tenzin *et al.*, 2011; Tran *et al.*, 2018; Yurachai *et al.*, 2020). The scanty study establishes the evidence in the literature that emerges from the population-based survey on the non-compliance rate (Lungten *et al.*, 2021).

The non-compliance proportion reported in a study conducted at the national level in Bhutan in 2008 is 40.4% (Tenzin *et al.*, 2011). A few years later, the finding is not much different, as, in a multi-centre study of 2014 to 2016, Vietnam had a similar result non-compliance rate at 58.6% (Tran *et al.*, 2019). A smaller scale of study in Haiti revealed that 45.4% had been discontinued Rabies PEV on their own (Tran *et al.*, 2018). The similarity of all the studies is the data collection involving multi-centre hospital-based patient records outspread across the country. Variation in sample size seems not to affect the non-compliance proportion as the sample size is approximately 110, 9000, 80000 in the study conducted in Haiti, Bhutan, and Vietnam, respectively (Tenzin *et al.*, 2011; Tran *et al.*, 2018, 2019). A study in India over a single institution presented that 46.8% of the animal bite patient fails to complete the vaccination course consistent with the findings in the similar study in Senegal with the proportion of non-compliance at 45.5% (Diallo *et al.*, 2019; Vinay *et al.*, 2013). All these studies conducted across all age groups that visited the institution during the study period.

All these findings contrast with the study by Romero-sengson (2013) conducted over the pediatric age group of the Philippines through an animal bite registry in a single institution. The study pointed out that the proportion of non-compliance even higher than all age group population, which is 88% pediatric animal bite patients receiving an incomplete vaccination series.

Lungten *et al.* (2021) manage to establish a shred of evidence for non-compliance rate based on the population survey out of abundant literature in the hospital-based setting. This study conducted over the school-children grade eight, nine, and 10 in the selected schools in the Rabies endemic area of South Bhutan through a self-administration questionnaire. The questionnaire design to access the knowledge and perception of Rabies. Out of 92 students who received the Rabies PEV over the past two years, only 3 (3.2%) did not manage to complete a series.

2.7 Factor associated with non-compliance of Rabies PEV

2.7.1 Age

Adults and children have different motivations to comply with the vaccination series. Parental concern plays a remarkable role in determining their children's compliance, especially under 15 years old, leading to a higher compliance proportion in this age group category (Tenzin *et al.*, 2011). On the other hand, adults might perceive barriers as loss of wages if they need to complete the vaccination over a series of timely and costly visits to the health centre (Shankaraiah *et al.*, 2015). On the other end, the elderly always happens to be the primary caretakers for the family dog. Having slightly better health-seeking behaviour could lead them to comply with the Rabies PEV series (Yurachai *et al.*, 2020).

Numerous past studies reveal that age has a significant role in ascertaining the non-compliance towards Rabies PEV, which age more than 15 less likely to complete the series (Diallo *et al.*, 2019; Penjor *et al.*, 2019; Yurachai *et al.*, 2020). In addition, the study in Bhutan stressed that the age 30 – 44 years old group more likely (Adj. OR = 1.29; 95% CI: 1.11,1.49; p-value < 0.001) to discontinued Rabies PEV without proper medical advice (Tenzin *et al.*, 2011).

2.7.2 Sex

Sex differences have been observed in the literature regarding risk perception and risk-taking behaviour (Reniers *et al.*, 2016). Non-compliance towards Rabies PEV is considered risk-taking behaviour and other medical non-compliance (WHO, 2012).

Tarantola *et al.* (2018) in a study on data collected from the Rabies Prevention Center (RPC) at the Institute Pasteur du Cambodge (IPC), in Phnom Penh, showed female was less likely to become non-compliers of the Rabies PEV (Adj. OR = 0.9; p-value = 0.006). This finding was consistent with the findings by the study in Thailand, in which males 1.3 higher odds (95% CI: 1.1,1.5; p-value = 0.008) to have incomplete vaccination series (Yurachai *et al.*, 2020). It might explain that in Asia, man synonym identity as the breadwinner for the family besides expected to be leaders and protectors (Sriyasak *et al.*, 2018). Thus, the perception of barriers to complete the Rabies PEV series due to scarcity of time for the healthcare facility visit and loss of wages lead them to focus on their duty as breadwinner (Haradanhalli *et al.*, 2019).

2.7.3 Ethnicity

Malaysia is one of the countries with multiethnicity in the community with a different background of behaviour. The establishment of the multiethnic society in Malaysia existed before independence attributed to nature and colonisation (Raja Sulong *et al.*, 2019). Thus, the different cultural backgrounds of each ethnicity lead to the report by N. F. Abdullah *et al.* (2019) as which ethnicity is one of the predictors for non-adherence.

Childhood immunisation adherence being utilised as a proxy to determine ethnic factors due to the similarity of the context of vaccination series. According to Krishna *et al.* (2019), ethnicity has unconditionally associate ($\chi 2 = 22.325$; df= 1; $p < 0.001$) with the children immunization defaulter. However, numerous studies reported no significant association between the ethnic group with the non-adherence of the childhood immunisation series in Malaysia (Abidin *et al.*, 2017; Ahmad *et al.*, 2017; Krishna *et al.*, 2019).

2.7.4 Education Level

Knowledge about Rabies is significantly differs based on the background of their education level. Those individuals with a better education level background tend to know Rabies rather than illiterate individuals (Palamar *et al.*, 2013; M. Sambo *et al.*, 2014). The smaller measure of education level as such difference grades in school demonstrates significantly associate with knowledge score of Rabies (Penjor *et al.*, 2019). Hence, it explained that education plays a part in the health literacy of Rabies and the importance of PEP compliance.

The study findings by Penjor *et al.* (2019) conclude that lower education less likely (OR = 0.46; 95% CI: 0.28,0.77: p-value = 0.003) to complete the Rabies PEV series. Besides that, the study in Dakar also has similar findings, which lower education status of family's head significantly associated (OR = 1.49; 95% CI: 1.12,1.98; p-value = 0.003) with partial Rabies PEP (Diallo *et al.*, 2019). It is not surprising that a similar phenomenon occurs in Malaysia, as supported by Krishna *et al.* (2019), suggesting that lower education status has a significant effect in lowering child immunisation rates.

2.7.5 Economic Status

The Rabies vaccine is expensive in certain countries, approximately USD 8 to USD 9 per dose of a single visit (Romero-sengson, 2013). In Thailand, a single dose of Rabies PEV costs about USD 48 to USD 64 to the patients, excluding indirect cost regardless of whether they receive intradermally or intramuscularly. That amount of cost relative equivalent to approximately equivalent to their five-day salary for an average resident. An entire complete series of Rabies PEV might cost a month salary (Yurachai *et al.*, 2020). In addition, indirect cost needs to be considered for a visit to complete the vaccine series, such as travel costs and income loss while attending health care facility (Diallo *et al.*, 2019).

It is unlikely for the people who are categorised as below the poverty line to afford at their own cost for the vaccine to complete the vaccination course. This scenario demonstrated in the study among pediatric patients in the Philippines that almost three-quarter of patients of the non-compliance towards Rabies PEV has the reason of unafforded (Romero-sengson, 2013).

Bariya *et al.* (2015) concluded that the Below Poverty Line (BPL) Cardholder has a significantly higher tendency (Adj. OR = 4.35; 95%CI: 1.34, 13.98; p-value = 0.013) to complete the vaccination series in India. It is not surprising that the vaccine services are given for free in India for this group compared to above the poverty line required to pay for the vaccine (Bariya *et al.*, 2015).

2.7.6 Type of Animal

The warm-blooded animal is known as an agent in the transmission of the RABV. The multifarious animal can be infected and transmit the RABV to humans. Nonetheless, the *Canis Lupus Familiaris*, known as domestic dogs, has been well established as the cause of human Rabies death globally. Thus, bit by the other animals such as cat, rodent creating lower perceived susceptibility towards compliance behaviour (Fooks and Jackson, 2020; Hampson *et al.*, 2015). This false perception of susceptibility is expected in the community even though the knowledge on the Rabies transmission well understood primarily in the frequent Rabies outbreak (Lungten *et al.*, 2021)

Type of animal significantly associated with completeness in which bitten by the animals other than dog and cat has lower odds (Adj. OR = 0.4; 95% CI: 0.3,0.6; p-value <0.001) to be non-compliance as compare to bitten by a dog (Yurachai *et al.*, 2020). Correspondingly, Tran *et al.* (2019) individuals who were bitten by a cat significantly have 17% lower chances (95% CI: 0.71,0.97; p-value < 0.05) of non-compliance than people whom a dog bit.

2.7.7 Dog Ownership

Non-compliance has been reported differently by the type of dog ownership in the literature. Due to a lack of awareness and understanding that pets can also be the reservoir for the Rabies, individuals exposed to an owned dog or often bite as part of play behaviour may have trivialised these exposures (Yurachai *et al.*, 2020). This perception of low susceptibility may affect the compliance of Rabies PEV. A surveillance study of Eastern Thailand showed that a person bitten by an owned dog has 60% higher chances (95% CI: 1.3,1.9; p-value < 0.001) to become non-compliance (Yurachai *et al.*, 2020).

On the other hand, a study conducted in Cambodia could not strengthen findings in Thailand as there was no significant association between dog ownership and incomplete Rabies PEV series (Tarantola *et al.*, 2018). The study in Cambodia was analysed the data from a single referral centre for the Rabies PEV, whereby the study in Thailand utilises electronic reporting platform R36 data that voluntarily used in seven Eastern Thailand provinces. The difference in the study setting might affect the interpretation of the association.

2.7.8 Category of Exposure

Category III of exposure accounted for 95% of the human Rabies death reported by the study in Bangladesh compared to Category II of exposure (Ghosh *et al.*, 2020). This piece of information shall generate a higher perception of severity that becomes the intention to comply with Rabies PEV (WHO, 2012).

On the other hand, a person with category I of exposure can express as "worried well" shall have a good sense of knowledge on Rabies and hyperalert on fundamental risk factors leading to compliance of the vaccine series despite it not recommended by WHO. However, it is difficult to conclude whether the phenomenon comes about because the providers prescribe indiscriminately or these "worried well" patients requested the vaccine (Tran *et al.*, 2019).

Previous studies in India showed that the category of exposure was not a predictor for the Rabies PEV compliance status (Bariya *et al.*, 2015). Astonishingly, Tran *et al.* (2019) reported that a person who classified as Category III exposure less likely to complete the Rabies PEV series as compared to those in category I of exposure (Adj. OR = 0.76; 95% CI: 0.61, 0.95; p-value < 0.05).

The main difference between these two studies was the length of the study and sample size. The study in India only takes place for eight months in two hospitals, and the small sample size (less than 250) in this study might not be enough to establish the association (Bariya *et al.*, 2015; Nemes *et al.*, 2009). Whereas the study in Vietnam by Tran *et al.* (2019) analyses over three years of data involving thousands of samples.

2.7.9 Site of Injury

The injury site was proven to have different lengths of incubation period that might reflect the needs for the completion of the vaccine, especially with those bitten in the head and neck (Guo *et al.*, 2018). Bitten on the head 11 timed higher tendency to contract human Rabies based on the findings in the Maputo and Mazola cities, Mozambique (Salomão *et al.*, 2017).

Multiple attempts for the researcher to establish evidence for the association of injury site with the non-compliance, yet the findings turn up not significant predictors for the compliance (Tarantola *et al.*, 2018; Tran *et al.*, 2019; Yurachai *et al.*, 2020). The sample size is not an issue to establish the evidence as the number of samples in these studies is more than enough from what has recommended for the observational study (Bujang *et al.*, 2018).

2.7.10 Year of Exposure

Two studies convincingly showed that exposure during the final year of the study period has significantly higher odds of becoming non-compliance than exposure during the first years of the study. The study in Bhutan initially has shown that almost twice the odds elevated (Adj. OR 1.96; 95% CI: 1.59,2.42; p-value < 0.001) and strengthen by the study in Cambodia, which tenth time higher odds (adj. OR = 10.00; 95% CI: 8.9,11.3; p-value < 0.001) to become non-compliance during the final year of exposure as compared to exposure during the first year of study (Tarantola *et al.*, 2018; Tenzin *et al.*, 2011).

It is happening in Bhutan as there were ongoing major Rabies outbreaks in Eastern Bhutan from 2005 to 2007 and Southern Bhutan in 2008. Comparing knowledge and practice between these two parts of Bhutan reveal that the southern part of Bhutan more likely to have ample knowledge on Rabies but less likely to have a favourable attitude towards Rabies control and prevention, consistent with the findings that the reason for not seeking PEP treatment as the patient has perceived low susceptibility due to bitten by a healthy owned dog (Beyene *et al.*, 2018; Rinchen *et al.*, 2019)

2.7.11 Type of Exposure

Clinical Rabies in animals is represented by the unpredicted and intermittent attacking without provocation due to the invasion of RABV into the central nervous system. Higher risk was perceived when exposure involving biting rather than the non-biting type of exposure (Fooks and Jackson, 2020). The classification of dog bites also includes the non-bite mechanism of transmission such as licking or scratching in the category of exposure where the bite type of exposure carries higher chances to develop human Rabies (Guo *et al.*, 2018; WHO, 2018b).

The non-bitten mechanism of injury was an unconditionally significant risk factor of non-compliance with Rabies PEV in the available current evidence (Tarantola *et al.*, 2018; Tenzin *et al.*, 2011). It might be explained by the motivation to complete the vaccine not a priority as the established evidence reported that deep wound has a higher tendency towards human Rabies compared to non-deep wound (Salomão *et al.*, 2017).

2.7.12 Type of attack

The term "provoked" was very controversial in the literature field. Despite that, several forms of human and dog interaction that elicit pugnacious behaviour in dogs have acknowledged. The dog's misapprehension of the dog's signal and unseemly attitude towards the dog in a risky condition often overlooked, especially in children, leads to the provocation of a dog bite (Mediouni *et al.*, 2020). It is well establishing that the furious form of Rabies in which the dog becomes irritable leads to aggressively bite and scratch (Fooks and Jackson, 2020).