Factors Associated with Vaccine Uptake: A Study on Rabies Post-Exposure Prophylaxis in The Philippines

OLADEJI K OLOKO

Thesis submitted in accordance with the requirements for the degree of Doctor of Philosophy of the University of London

DECEMBER 2023

Department of Infectious Disease Epidemiology
Faculty of Epidemiology and Population Health
LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

School of Tropical Medicine and Global Health
NAGASAKI UNIVERSITY

Funded by the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) WISE Program

Research group affiliations: The Vaccine Confidence Project &
SLH - Nagasaki University Collaborative Research Office

Declaration

I, Oladeji K Oloko, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Acknowledgements

Thank you to my supervisors Chris Smith and Pauline Paterson for their guidance and patience. I could not have imagined all the obstacles I would be faced with, and I am grateful to them for supporting me in the face of an unexpected PhD journey. I would not have achieved this body of work without their invaluable expertise and insights.

Thank you to Nagasaki University and LSHTM for the academic opportunities and funding. Working on a PhD across two culturally distinct institutions has taught me resiliency and flexibility.

I'm incredibly grateful to the San Lazaro Hospital team for welcoming me in and supporting my research in the Philippines. A special thank you to Jack Suzuki, Mean Salazar, Dr Ana Ria Sayo, Ms Lorraine Abaya and Dr Ferdinand de Guzman. Greco, we didn't work together directly but I'm grateful for your encouragement and friendship.

Thank you to the healthcare providers and patients who took time to contribute to this PhD as study participants. Research is first and foremost for the target populations. It is fundamentally centred around and meant to benefit them, and I am grateful for their participation.

PhDs can be a solitary time, especially during a pandemic, so I'm lucky to have had the EPH and Nagasaki PhD groups to turn to including Anne, Su, Rutendo, Abdoulie, Lauren and Susan. Your friendships, whether through zoom calls or coffee breaks, definitely prevented breakdowns.

The past four years were intense and overwhelming. I'm so fortunate to be surrounded by people who helped me get to the end:

To Sarina, Erica, Pelumi, Caroline, and all the friends who saw more in me when I lost confidence and the ability to dream. Thank you for cheering me on, pushing me, and believing the best parts of me were still there.

Ruthly and Jessica, I wouldn't have even begun this PhD without your support, your advice, and you holding me through that tough period. I love you both and love that we'll be doctors together.

Abiola and the Orpington crew, thank you for feeding me, for being my home, and for the kids that bring such immense joy that even the darkest PhD day could not dampen.

Khalil, we both got to the end of these agonising thesis months. I know it's not easy, but I believe if I could get to the end of this, you can conquer your goals.

To my parents who instilled in me the hunger for success and provided the best educational foundation I could have dreamed of, thank you for the prayers and the unconditional, unwavering love. Mami, your phone calls are like sunshine. Papi, you have a Dr Oloko!

To my sister Femi, this PhD is because of you. There are no words that could accurately describe how lucky I am to have you. You held me up, kept me going, and stayed by my side when I wasn't sure I would make it. Sometimes all that we need in life is someone who shows up for us every day, I'm endlessly grateful I have that in you.

Abstract

Introduction

Rabies, a fatal vaccine-preventable disease, is endemic in the Philippines. The national rabies program aims to offer free vaccination using a 3-dose schedule when WHO-prequalified vaccine is available and 4 doses when not. The PhD objectives were to quantify vaccine adherence, explore immunisation attitudes, assess factors associated with uptake, and understand facilitators and barriers to completion.

Methods

Four studies were conducted at San Lazaro Hospital (SLH)'s animal bite treatment centre (ABTC), Manila. A formative observation study including in-depth interviews with providers contextualised the ABTC. A retrospective database analysis and a prospective mixed-method cohort study assessed vaccine completion and factors associated with adherence. The final study surveyed rabies-exposed individuals to investigate failure to initiate vaccination.

Results

Over 300,000 patients accessed the SLH ABTC between 2016 and 2021, 27% of whom completed vaccination. The prospective study of 506 participants reported 86% vaccine completion. Females and participants aged 60+ had higher odds of adherence. The main barriers to vaccine uptake were a lack of time, the inability to access ABTCs when travelling outside Manila, and forgotten schedules. Major facilitators to vaccine uptake were high confidence in rabies vaccine and the influence of individuals' social networks.

Highlights

This PhD reported three novel observations: 1) clinics and healthcare providers can be deterrents to rabies vaccine completion, 2) individuals' social networks influence rabies vaccine uptake and can be leveraged to improve vaccine adherence, 3) travelling outside Manila is a frequently reported barrier to vaccine completion.

Conclusion

This PhD underscored the need to improve vaccine uptake. While vaccines may be provided free, costs such as travel, and the loss of productive time and wages, are barriers to vaccine uptake. It is essential to evaluate access to ABTCs across the country and institute the permanent use of WHO-prequalified vaccines to increase vaccine completion.

Table of Contents

List of Tables

List of Images and Figures

Abbreviations

ABTC	Animal bite treatment centre
aOR	Adjusted odds ratio
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CNS	Central nervous system
DOH	Department of Health of the Republic of the Philippines
ECQ	Enhanced community quarantine
EPI	Expanded Program on Immunisation
ERIG	Equine rabies immunoglobulin
GCQ	General community quarantine
HBM	Health Belief Model
HCP	Healthcare provider
HDCV	Human diploid cell vaccine
HRIG	Human rabies immunoglobulin
IBCM	Integrated bite case management
ID	Intradermal
iHOMIS	Integrated hospital management information system
IM	Intramuscular
IPC	Institut Pasteur Cambodia
IQR	Interquartile range
KAP	Knowledge, attitudes and practices
LMICs	Low- and Middle- Income Countries
MCHD	Manila City Health Department
NaRIS	National Rabies Information System
NCR	National Capital Region
NRPCP	National Rabies Prevention and Control Program
NTD	Neglected tropical disease
OPD	Outpatient department
OR	Odds ratio
PCECV	Purified chick embryo cell vaccine
PEP	Post-exposure prophylaxis
PHP	Philippine peso (₱)
PreP	Pre-exposure prophylaxis
PVRV	Purified Vero cell rabies vaccine
REF	Reference variable
RIG	Rabies immunoglobulin
SAGE	Strategic Advisory Group of Experts on Immunization
SES	Socioeconomic status
SLH	San Lazaro Hospital
VCP	Vaccine Confidence Project
WG	Working Group
WHO	World Health Organization

Overview of Thesis

This thesis presents the body of work carried out throughout the PhD, which aimed to quantify, understand, and characterise rabies vaccine uptake in the Philippines. The study objectives were derived from the working hypothesis that there are demographics, rabies exposure factors, or knowledge, attitudes and practices, which influence vaccine uptake. It is a combination of research paper style and traditional chapter style thesis. Chapter 1 contains a background on rabies disease including its pathology, transmission, epidemiology, prevention strategies, and vaccine use. Chapter 1 also presents theoretical models of vaccine decision making. Chapter 2 provides the PhD project introduction describing aims and objectives, the project site, other project particulars, and a brief overview of the research studies. Chapter 3 contains a literature review, detailing published research relevant to the thesis aims. The following chapters 4 to 7, then contain the research studies. Study 1 and 3 are research paper style, written as manuscripts to be submitted for publication, while Study 2 and 4 are chapters contained solely within this PhD thesis. Chapter 8 is the discussion chapter which provides overarching conclusions and recommendations. Chapter 9 contains references. Data collection instruments are presented in Chapter 10.

1 Background

1.1 Rabies Disease: Transmission, Pathogenesis, Clinical Presentation and Diagnosis

Rabies, a neglected tropical disease (NTD), is a fatal zoonotic viral infectious disease of the central nervous system (CNS) [1, 2]. It is caused by the rabies virus, a negative-stranded RNA virus, of the *Lyssavirus* genus [3]. Infection typically occurs through an open wound; the virus then propagates along nerve tissue to the brain and into the CNS [4]. The rabies virus glycoprotein is a transmembrane protein which binds to the host's cell receptors during infection, leading to invasion of the CNS [5]. The interactions between the glycoprotein and human cell receptors are not fully understood [5, 6], however studies have investigated a number of cell-surface receptors which the glycoprotein binds to; nicotinic acetylcholine receptor [7] [8], neural cell adhesion molecule [9], low-affinity nerve-growth factor receptor (p75NTR) [10], metabotropic glutamate receptor subtype 2 [11], and integrin β1 [12]. Following infection of the brain and CNS, the virus spreads through the peripheral and autonomic nervous systems and finally into the salivary glands, where the transmission cycle continues; a bite from an infected animal transfers the virus into the new host through saliva [13].

While natural infection most commonly occurs via an animal bite, aerosolised transmission has been noted in accidental aerosolization of the virus in laboratory settings and bat caves [14]. Human to human transmission has been documented in tissue transplants, initially found in cases of corneal transplants where both the recipient and the donor died and were retrospectively diagnosed with rabies, and also in accidental blood exchange [15-17]. Due to human rabies being eliminated in many countries and its status as a neglected disease, low awareness of human infections in nonendemic countries has led to these incidences of fatal

tissue transplants [1]. It is important to increase awareness of rabies to prevent pathogen transmission [1]. Transmission through human bites and consumption of infected animals is theoretically possible but has not been confirmed [15, 18]. Although cases due to consumption have not been reported in published literature, there are reported cases linked to slaughterhouse activities [19]. Additionally, rabies cases due to immunisation with improperly inactivated vaccine have been recorded [20].

In rabies-infected non-human animals, clinical signs include lethargy, fever, vomiting and anorexia. Signs progress within days to cerebral dysfunction, weakness, excess salivation, abnormal behaviour, and paralysis. Death usually occurs within two weeks of symptom onset in dogs. The characteristic description of a rabid animal exhibiting aggression is due to viral neuroinvasion which leads to excitation of the CNS [21]. All warm-blooded vertebrates are susceptible to rabies infection but the natural reservoir is primarily mammals [22]. Dogs are the main reservoir species of human consequence, causing ninety-nine percent of all rabies deaths [23]. In countries where comprehensive canine vaccination programs are in place, wild animals such as bats, foxes, and racoons are the main reservoirs [24]. Marsupials have shown high disease resistance in both experimental infection and occurrence of wild cases, indicating that disease susceptibility differs amongst species [25].

Exposure to a rabies infected animal can lead to pathogen transmission but the rabies risk therein varies by the exposure type. An indoor pet carries lower risk than a stray dog with unknown vaccination history and contacts, a scratch less risk than multiple bites, and the location of the bite on the body also affects rabies infection risk [20, 23, 26]. Without prophylaxis, an estimated 30-60% of people bitten on the neck, head, or face develop rabies, this reduces to 15-40% in individuals bitten on the hand, while the lowest mortality

risk at 0-10% is in those with bites on the trunk and leg [27]. These differing risks lead to exposure classification in three categories which designate required post-exposure prophylaxis [18], and will be discussed further in Section 1.4.

In humans, rabies infection follows five phases: incubation, the prodrome (early nonspecific symptoms), acute neurological phase, coma, and death.

1. Incubation: The incubation period of rabies infected patients ranges from a week to six years, however most patients present symptoms within one to three months. The length of the incubation period is dependent on the infection site, virus strain and viral load. Shorter incubation periods are observed in patients with multiple bites and bite sites closer to the brain. The shortest incubation periods are in patients with multiple severe facial bites. [20, 28]
2. Prodrome: The asymptomatic incubation period is followed by the prodromal phase characterised by nonspecific symptoms such as anxiety and mild flu-like illness including fever, headache, fatigue etc. Neuropathic pain presenting as itching or numbness at the bite site may occur as the first specific clinical symptom. The prodromal phase can last up to a week. [28, 29]
3. Acute Neurological Phase: Upon symptom onset, the mild prodromal phase progresses rapidly to a furious or paralytic presentation. Furious rabies, seen in 65-70% of patients is characterised by hallucinations, periods of hyperactivity, and the classical diagnostic symptoms of hydrophobia and aerophobia. Periods of hyperactivity, aggression and altered mental status last one to five minutes and alternate with lucid intervals. Paralytic rabies is less common and harder to

diagnose. It is characterised by weakness, loss of sensation at the bite site, and paralysis. It is more frequently linked to bat exposures. [28, 30]

4. Coma: Following the acute neurological phase, raised intercranial pressure due to inflammation of the brain leads to a coma. [28, 31]
5. Death: While the patient is comatose, death occurs due to cardiac or respiratory failure. [28]

Rabies has a case fatality rate approaching 100%, the highest of any infectious disease. Survival from rabies has been documented in a rare number of cases, 27 patients have been reported in published literature as of 2020 [32]. Majority of these patients had received at least one dose of the rabies vaccine prior to onset of clinical disease. Two patients made complete recoveries while most of the survivors recovered with severe disabilities, including neurological sequelae [32].

Rabies is clinically diagnosed by exposure history and symptoms in the prodromal and acute neurological phases. The most accurate diagnostic test for rabies is post-mortem analysis of tissue from the brain stem and cerebellum for viral antigens. Ante-mortem diagnosis in humans requires viral RNA detection in multiple skin biopsy or saliva samples [5]. Due to intermittent shedding of the virus in saliva, a negative test cannot conclude a patient is uninfected. The presence of rabies-specific antibodies in unvaccinated patients can also be used as a diagnostic tool [20, 30]. As diagnosis does not lead to improved prognosis, laboratory tests are not often carried out in low resource settings [26]. Due to this, rabies, especially paralytic rabies, is often misdiagnosed as other encephalitis causing conditions including Guillain–Barré syndrome [2] and cerebral malaria in tropical countries [23, 33].

Furthermore, due to neurological symptoms, patients have also been misdiagnosed with strokes [20] and psychosis [34, 35].

Upon the onset of clinical symptoms in the prodromal phase there are no effective treatment options, however rabies is preventable with vaccination. Rabies differs from other vaccine preventable diseases; its vaccine can be delivered prior to an exposure, as pre-exposure prophylaxis (PrEP) or immediately after, as post-exposure prophylaxis (PEP). The existing vaccine regimens for rabies are almost 100% effective when administered in a timely manner, and has been estimated to avert 280,000 deaths a year globally [36]. Due to the highly effective vaccine and the fatal nature of the disease, the standard of care for all persons suspected of rabies exposure is immediate administration of PEP [20].

The first step in post-exposure care is washing of the wound with soap and water. Following wound care, passive and active immunisation, i.e. rabies immunoglobulin (RIG) and inactivated virus vaccine respectively, are used [20]. Dependent on the schedule in use and if patients are vaccine-naïve, three to five vaccine doses are required for an adequate immune response [37, 38]. In addition to rabies vaccination, tetanus vaccination and antibiotics are administered, as necessary. Rabies prevention will be discussed further in Section 1.3.

As there are no effective treatment options available, clinical management of rabies is mainly palliative. However, fear of rabies is common among health-care providers which can result in relatively poor care [20, 39]. In resource-rich settings, palliative care consists of administration of sedatives and anticonvulsants [40], however in low-resource settings where essential medicines are scarce, patients are often hospitalised in isolation rooms with security bars, and strapped to the bed as a precaution for the periods of hyperactivity in

furious rabies [39]. Image 1.1 shows two isolation rooms in the Philippines. Fooks et al. present clinical videos of a paediatric rabies case in the Philippines displaying hydrophobia [41].

Image 1.1 Rabies isolation rooms in the Philippines

In rare cases, treatment of rabies patients has been attempted. The first recorded case of recovery was in 1970 [42], followed by four further documented cases, however all patients recovered with severe sequalae [8, 43-47]. Recovery was more common in patients that had received at least one vaccine dose pre- or post- exposure and those bitten by bats, which has led to speculation that canine rabies virus variants are more neurovirulent than bat variants [48, 49]. In 2004, a 15-year-old with no history of rabies vaccination sustained a small finger laceration from a bat. A month later, she presented with symptoms and the

clinical diagnosis was confirmed by the presence of rabies antibodies. She was placed in a ketamine induced therapeutic coma and administered antivirals. The patient survived, although with severe disabilities, and the treatment plan has been dubbed the Milwaukee protocol [50]. A review on the use of the Milwaukee protocol and revised versions, found it had been trialled in thirty-eight patients between 2004 and 2019, eleven of whom survived [51]. As rabies virus or antibody were not detected in the survivors, doubts in the initial rabies diagnoses arose, and therefore there have been no confirmed rabies recoveries since the initial use of the Milwaukee protocol [52]. Due to the many failures, there have been critical reviews of its use and recommendations that the approach be abandoned [53-56]. As current therapeutic options have had limited success, research into molecules with antiviral capacity to prevent death after the onset of rabies disease are continuously being investigated, however none have reached human trial stages [57, 58].

1.2 Rabies Epidemiology

Global Outlook on Rabies

Globally, rabies causes an estimated 59,000 deaths per year [95% CI: 25,000–159,200] [23]. However, the global burden of disease is likely an underestimate due to a variety of factors; underreporting, misdiagnosis and poor surveillance. These issues lead to limited capacity to accurately estimate disease incidence and mortality [59]. As countries across North America, Europe and Australasia have largely eliminated canine rabies, the greatest number of deaths occur in Asia and Africa, 60% and 36% of the global burden of death, respectively. While the per capita death rate is highest in African countries such as the Democratic Republic of Congo and Zimbabwe, the highest total burden of disease is in Asia. India and China have the highest estimated total deaths per country, 21,000 and 6,000 respectively [23]. The estimated annual rabies incidence is 3.6 per 100,000 in Africa, although some estimates are

closer to 13 per 100,000 [20, 60] while there an estimated at 0.8 per 100,000 person deaths in Asia [61]. An estimated 3.7 million disability adjusted life years (DALYs) are lost due to rabies globally, most due to years of life lost [95% CI: 1.6–10.4 million] [23].

It is difficult to accurately estimate the true burden of disease in countries without robust active surveillance systems. However, the World Health Organization (WHO) estimates the occurrence of tens of millions of dog bites annually which translates to a high risk of rabies exposure in countries where canine rabies is endemic [62]. Approximately 80% of rabies cases occur in rural low-income settings and 40% of cases occur in children aged five to fourteen [18].

The basic reproductive number, R_0, was estimated at 1.1 to 2.0 secondary infections produced by an infected dog in a fully susceptible population [63]. This estimate predicts that a vaccine coverage of 20-45% may be adequate to eliminate rabies [23]. Due to dog populations with high turnover, it is necessary for annual vaccine campaigns to achieve vaccine coverage of 70%, to sustain herd immunity and interrupt rabies virus transmission [63-66].

The global economic burden of rabies is estimated at 8.6 billion USD annually. The main costs are due to productivity losses from premature deaths (2.27 billion USD), direct expenditure on PEP (1.7 billion USD), and income lost while seeking PEP (1.31 billion USD). Other costs include vaccination of domestic dogs and livestock deaths [23, 67].

Rabies in The Philippines

Phylogenetic analyses of rabies virus strains have shown that rabies was introduced into the Philippines from China at the beginning of the 20th century [68]. The first laboratory confirmation of a canine rabies case occurred in 1910 [69]. Prior to this, doctors in Manila

had recorded incidences of hydrophobia leading to deaths from 1902 [69]. Despite the initial legislature passed for rabies control, Act No. 2461 Rabies Law of 1915 [69], and other control efforts there are still an estimated 377 rabies deaths in the Philippines annually, an incidence of 0.34 per 100,000, last estimated in 2019 [70]. This is likely an underestimate. In 2017, there were an estimated 363 rabies deaths in the Philippines based on modelling by the Institute for Health Metrics and Evaluation (IHME) [70], while the total number of reported cases published by the Philippines Department of Health (DOH) was 262 [71]. In 2017, San Lazaro Hospital (SLH), Manila, recorded 51 clinically diagnosed cases, extracted from the hospital's mortality database. SLH serves the National Capital Region (NCR), a population of 13.5 million [72]. While serving an eighth of the Philippines' population, SLH reported a fifth of the recorded cases. Furthermore, the NCR has higher education levels and socioeconomic status, and the residents have better access to medical care, and likely a higher knowledge and awareness of rabies to recognise disease symptoms. It can be concluded that it is likely that there are cases which go unreported, especially in underserved areas of the Philippines. Therefore, the reported case numbers are likely below the true rabies incidence in the Philippines. Furthermore, it is likely that this is reflected in countries across the world and this misdiagnosis and poor surveillance leads to an underestimation of the global burden of disease.

Canine rabies is endemic and there are a rising number of animal bites reported annually to the Philippines Department of Health (DOH), in excess of one million in 2019 [73]. Some studies report a bite incidence ranging from 0.49-0.67 per 100,000 per year [74]. Therefore, the rabies risk is likely higher than that reflected by the total estimated annual deaths. However, the rising bite incidence may also be attributed to improved reporting and

increased healthcare seeking behaviour as animal bite treatment has been free in the Philippines since 2016 [73].

Despite having a free post-exposure prophylaxis program, rabies incidence in the Philippines is the fifth highest in Asia behind Myanmar, Pakistan, Nepal, and India [70]. This can be attributed to the high population density in large cities and high pet ownership in the Philippines. 83% of the population owns a pet, higher than the continental average of 59%, the highest in Asia [75]. 67% of Filipinos own dogs [75], and these are often free roaming dogs. A 2022 study across a province in the Philippines estimates 31% of dog-owning households allow their dogs to roam free [76]. Free-roaming dogs can lead to large unmanaged dog populations with high turnover rates which hinders canine vaccine coverage. Therefore, rabies virus transmission is often higher in environments with free-roaming dogs [65, 66].

In line with global trends, rabies disproportionately affects children in the Philippines with a third of all deaths occurring in children under fifteen years old [77]. Men are 2.5 times more likely to die from rabies, and deaths have been reported to be associated with municipalities and regions with higher income, although the reasons behind this are speculative [78].

Table 1.1 presents rabies deaths across regions of the Philippines reported to the DOH. The highest number of deaths occurred in Region 3 (Central Luzon) and Region 4A (Calabarzon). These regions have the third highest and highest populations, respectively [79].

Region No.	Region Name	2014	2015	2016	2017	Total
3	Central Luzon	29	29	39	50	147
4A	Calabarzon	49	31	37	32	149
12	Soccsksargen	27	21	19	34	101
5	Bicol	16	25	22	18	81
1	Ilocos	21	24	19	10	74
11	Davao	21	16	15	10	62
NCR	National Capital Region	21	22	10	10	63
7	Central Visayas	3	10	15	21	49
6	Western Visayas	10	15	11	19	55
10	Northern Mindanao	12	16	16	11	55
9	Zamboanga Peninsula	15	8	11	10	44
2	Cagayan Valley	19	10	7	5	41
16	CARAGA	10	11	11	7	39
8	Eastern Visayas	7	5	10	12	34
4B	Mimaropa	4	0	4	5	13
ARMM	Bangsamoro	1	2	6	3	12
14	CAR	1	0	7	5	13
	Philippines	**266**	**245**	**259**	**262**	**1032**

Table 1.1 Reported rabies cases by region based on place of exposure [71]. See Image 2.1 for regional map.

1.3 Rabies Prevention Strategies & Policy

Global Rabies Prevention

In 2017, the World Health Organization (WHO) created a neglected tropical diseases (NTD) roadmap for global elimination efforts. It targets a reduction of dog-mediated rabies deaths to zero by 2030 [80]. The rabies prevention strategy developed by the WHO and the World Organisation for Animal Health (OIE) relies on three components [18]:

1. *Animal management and canine vaccination programs*

   Interrupting rabies transmission requires prevention of rabid bites. This can be achieved through animal management including the rehoming of strays or culling programs, and canine vaccination. Individual costs of canine vaccination ranges across the world from £6/dose in some West African countries to £0.35/dose in the Philippines and £0.20 in Tanzania. The most cost effective method of rabies prevention is dog vaccination [23].

2. *Education and community awareness*

   Education on dog behaviour, bite prevention, and care following a bite are essential to the rabies prevention program. This has been done through global and national campaigns including school-based education [81].

3. *Integrated bite case management (IBCM) and human immunisation*

   IBCM includes the identification of potentially rabid animals, contact tracing of suspected rabid animals and human bite victims, and post-exposure care of bite victims. PEP is the most used form of rabies vaccination while PreP is used in high-risk occupations and travellers from high-income countries to endemic regions [82]. Rabies vaccine doses range from £10–120, manufacturer and country dependent. Some countries have established free PEP programs.

Rabies Prevention in The Philippines

In 2007 the Philippines Anti-Rabies Act established prevention and control programs including canine vaccination, education campaigns, and provision of human vaccines. The National Rabies Prevention and Control Program's (NRPCP) goal is to end dog-mediated rabies deaths by 2027 and achieve a rabies free Philippines by 2030. Human rabies is classified as an immediately notifiable disease and must be reported within 24 hours to the DOH's epidemiology bureau [73].

A national canine vaccination guideline for pets was established and mass dog vaccination is carried out by the Department of Agriculture yearly. The pet guidelines are akin to countries in Europe and the Americas, however high vaccine coverage has not been achieved in dog populations, with an estimated coverage of 53% in 2018 [83]. A target of 70% vaccine

coverage during annual mass dog vaccine campaigns is essential for rabies elimination in free-roaming dog populations that are highly dynamic [63, 84].

Health promotion activities are carried out by celebrations of rabies awareness days, distribution of educational flyers, health information campaigns on news media, and rabies education in school programs [73]. In 2016, the Anti-Rabies Act was expanded by the NRPCP to provide PEP across the country through the establishment of a decentralised network of animal bite treatment centres (ABTCs). The DOH aims to offer increased access by providing 1 ABTC per 100,000 people for the Philippines' 110 million inhabitants [85]. Free PEP vaccine and subsidized rabies immunoglobulin (RIG) are provided at ABTCs, however, where there are stockouts of government supplied vaccines, patients have been required to purchase vaccines from personal funds [74]. Through these mechanisms, the DOH expects to increase vaccine uptake in rabies exposed individuals and aims to ensure 90% of rabies vaccine series are completed [73]. This will contribute to reaching the end goal of a rabies free Philippines by 2030.

1.4 Rabies Vaccine

Rabies Vaccine Development and Global Recommendations

As of 2023, the WHO estimates that more than 29 million people worldwide receive a post-bite rabies vaccination every year, preventing hundreds of thousands of rabies deaths [18]. The first rabies vaccine, an inactivated nerve tissue vaccine, was developed in 1885 by Louis Pasteur and Emile Roux [86]. It was first administered as twelve doses over two weeks [87]. The production, schedule of doses, availability and cost has changed considerably since then. Nerve tissue vaccines were replaced by safer and more immunogenic duck embryo vaccines and later, human diploid cell vaccines [86]. Protection against rabies infection is

mediated by virus neutralizing antibodies against the glycoprotein expressed on the surface of rabies virus [88]. The correlate of protection is assessed by antibody titres of at least 0.5 IU/ml [89].

There are currently four WHO prequalified rabies vaccines [90, 91];

1. Purified Vero Cell Vaccine (PVRV) 1 ml/vial [RABIVAX-S, Serum institute]
2. Purified Chick Embryo Cell Vaccine (PCECV) 1 ml/vial [Rabipur/RabAvert®, GSK]
3. Purified Vero Cell Vaccine (PVRV) 0.5 ml/vial [Verorab®, Sanofi]
4. Purified Chick Embryo Cell Vaccine (PCECV) 1 ml/vial [VaxiRab N, Zydus]

These vaccines offer strong protection and have a good safety profile. Reported adverse events are mild side effects such as pain at injection sites, sore arm, headache or fever [20]. All rabies vaccines in use were developed to be administered via intramuscular (IM) injection. However, immunogenicity studies have shown that intradermal (ID) administration is effective, and with a smaller dose requirement of 0.2ml as opposed to the use of a full vial, ID administration lowers vaccination costs by 60-80% [92-94]. The WHO recommends immunocompromised patients receive vaccines through IM administration to ensure immunity is conferred [95].

Due to the highly optimised immunogenicity and safety of these approved vaccines, current rabies vaccine research is focused on forms of administration to reduce dosage and costs [96]. An array of protein subunit, mRNA, DNA, adjuvanted vaccines, and adenovirus-vectored vaccines are being evaluated [96], the latter of which would require a single dose only [97]. This would significantly reduce immunisation program costs and therefore have the potential to reach more rabies-exposed individuals [97].

Rabies vaccination in the form of pre-exposure prophylaxis (PreP) is primarily used in individuals with high-risk occupations and travellers from non-endemic countries [98]. The use of PreP in childhood immunisation schedules has been considered but deemed cost ineffective with the current dosage requirements and vaccine prices, except in endemic settings where bite incidence is 30% or higher [95, 98, 99]. With high bite incidence in countries like the Philippines, studies have evaluated and modelled the use of a school-based PreP program which showed the potential for cost savings and additional deaths adverted [81, 100]. For the potential use of rabies PreP in childhood immunisation schedules, there has been a proposal to develop a multivalent vaccine adding rabies antigen to the current measles, mumps rubella (MMR) vaccine [101].

Rabies immunoglobulin (RIG), given to severe exposures, is infiltrated around the wound with a dosage of 20 IU/ Kg for human RIG (HRIG), and 40 IU/ Kg for equine RIG (ERIG). ERIG which is cheaper, is often used in low resource settings, although there is higher risk of hypersensitivity reactions. While not recommended by the WHO, as it is considered a poor predictor of adverse effects, skin tests are often carried out in certain LMICs before the administration of ERIG. Patients who are reactive are therefore administered HRIG [95].

Current research is pursuing the development of monoclonal antibodies to replace RIG as blood derived products are expensive and laborious to manufacture [102]. One product has been licensed in India and has shown safety in phase IV trials [103, 104]. Monoclonal antibodies of mouse origins have also been investigated as a potential alternative to RIG [102]. A study conducted by Müller et al reported that a cocktail of selected mouse monoclonal antibodies which bind to the rabies virus glycoprotein resulted in protection *in vivo* with equal efficacy to HRIG [105]. Further cocktails of mouse monoclonal antibodies

have been investigated and advanced to clinical trials [104]. In addition to identifying efficacious monoclonal antibodies, there have been efforts to lower industrial production costs by improving productivity of cell lines [106], and the use of less expensive production systems including transgenic plants and cell cultures which can express anti-rabies monoclonal antibodies [107]. Transgenic plants which would produce "plantibodies" could be grown in large scale greenhouses reducing manufacturing costs [102].

Upon presentation of a potentially rabies exposed patient, the exposure of risk is classified into three categories, as shown in Table 1.2, which determines the recommended PEP and vaccination schedule.

Categories of Contact with Suspected Rabid Animal	**Post-Exposure Prophylaxis (PEP)**
Category I (no exposure) – touching or feeding animals, animal licks on intact skin	Washing of exposed skin surfaces, no PEP
Category II (exposure) – nibbling of uncovered skin, minor scratches, or abrasions without bleeding	Wound washing and immediate vaccination
Category III (severe exposure) – 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	Wound washing, immediate vaccination, and administration of rabies immunoglobulin

Table 1.2 Categories of rabies contact and recommended PEP [18]

The current WHO recommended vaccine schedules for immunologically naïve individuals with a rabies exposure are as follows:

a) "Institut Pasteur Cambodia (IPC) 2-2-2-0-0" (2-sites ID on days 0, 3 and 7; total duration 7 days)
b) "Essen 1-1-1-1-0" (1-site IM on days 0, 3, 7 and between days 14–28; total duration up to 14–28 days), or
c) "Zagreb 2-0-1-0-1" (2-sites IM on day 0 and 1-site IM on days 7 and 21; total duration 21 days).

Two sites refers to the administration of a vaccine dose in each arm. Table 1.3 provides further details on the use of these schedules by the category of exposure, and in immunologically naïve or previously vaccinated individuals. Rabies vaccination provides long term B-cell memory and therefore booster doses, using the schedule described below for previously vaccinated individuals, are efficient in restoring antibody to protective levels. Additionally, there have been studies showing antibody persistence up to thirty-two years after a full post-exposure schedule of the HDCV [108].

	Category of Exposure		
	Category I	Category II	Category III
Immunologically naïve	Wash exposure site. No PEP required	Wash wound & vaccination. 2-site ID on days 0, 3, 7[a] **OR** 1-site IM on days 0, 3, 7, & between day 14-28[b] **OR** 2-site IM on day 0 & 1 site IM on days 7, 21[c]	Wash wound, vaccination & RIG. 2-site ID on days 0, 3, 7[a] OR 1-site IM on days 0, 3, 7 & between day 14-28[b] **OR** 2-site IM on day 0 & 1 site IM on days 7, 21[c]
Previously immunised	Wash exposure site. No PEP required	Wash wound & vaccination.[d] 1-site ID on days 0, 3 **OR** 4 site ID on day 0 **OR** 1-site IM on days 0, 3	Wash wound & vaccination.[d] 1-site ID on days 0, 3 **OR** 4 site ID on day 0 **OR** 1-site IM on days 0, 3

a One-week, 2-site ID regimen (Institut Pasteur Cambodia (IPC) 2-2-2-0-0) total duration 7 days
b Two-week IM regimen (Essen 1-1-1-1-0); total duration 14–28 days
c Three-week IM regimen (Zagreb 2-0-1-0-1); total duration 21 days
d Vaccination is not recommended if complete PEP received within <3 months

Table 1.3 WHO recommendation for rabies PEP by category of exposure. Adapted from Rabies Vaccine: WHO Position Paper [95]

Rabies vaccine should be administered immediately after exposure, hence the first dose being “Day 0”. However, if a category III exposure presents even months after exposure, rabies vaccine should be administered. As the likelihood of development of clinical rabies declines significantly after 12 months, in the case of limited supplies, vaccines can be reserved for patients presenting within the 12-month post-exposure window [95]. Rabies

vaccine can be discontinued if the animal of exposure is a domestic animal and remains alive throughout a 10-day observation period [95].

While rabies PEP is highly effective, some deaths in patients who received PEP have been reported. These are generally linked to deviations from recommendations including the lack of, or improper administration of RIG in severe category III exposures, and are therefore not considered true vaccine failures [20, 109, 110]. Rabies patients with a history of appropriate wound management, RIG and vaccine are rare but have been documented. These cases often received multiple bites on the face and upper body [111-113].

Rabies Vaccination in The Philippines

In 2018, the Philippines changed its national guidelines to match the WHO's ID administration recommendations [73]. The IPC schedule (6 doses via 2 sites on 3 days. Days 0, 3 & 7) is used for prequalified vaccines, however from 2018 until 2022 there were shortages of prequalified vaccines, therefore the updated Thai Red Cross schedule has been in use, which requires two additional doses on day 28, for a total of 8 doses via 2 sites on 4 days. This is due to concerns that non-prequalified vaccines are insufficiently immunogenic and may not confer complete protection using the seven-day schedule. The current PEP recommendation is shortened to 3 doses if the biting animal is still alive after 14 days. Immunocompromised patients are recommended the Essen schedule (5 doses via 1 site on 5 days. Days 0, 3, 7, 14 & 28) [73]. The recommendations are summarised in Table 1.4. Rabies vaccine has been provided free in ABTCs across the Philippines since 2016, while RIG is subsidized [82].

RIG costs are approximately 2,400 to 14,000 PHP (£36-215) to the patient. Equine- and human- RIG vials are approximately 1,200 PHP (£18. 5ml, 1,000 IU [114]) and 3,500 PHP

(£53. 2ml, 300 IU [115]), respectively. Using the maximum dose calculation for RIG administration of 40 IU/ kg for equine and 20 IU/ kg for human RIG [95], and an average adult weight of 60kg [116], patients require 2,400 and 1,200 IU respectively therefore two or four vials are often used.

	Categories of Contact with Suspected Rabid Animal		
	Category I	Category II	Category III
Immunologically naïve	Wash exposure site. No PEP required[2]	Wash wound 2-site ID on days 0, 3, 7, 28[3,4]	Wash wound 2-site ID on days 0, 3, 7, 28 RIG[5]
Previously vaccinated[1]	Wash exposure site. No PEP required	Wash wound 1-site ID on days 0, 3 **OR** 4 site ID on day 0	Wash wound 1-site ID on days 0, 3 **OR** 4 site ID on day 0
1 - PrEP or PEP days 0 & 7. Vaccination not recommended if PEP completed <3 months 2 - Antibiotics & tetanus vaccine may be administered 3 - 3 doses only for WHO pre-qualified vaccines 4 - 4th dose is not administered if the biting animal is alive on day 14 5 - Human RIG is used if reactive to equine RIG Immunocompromised patients with category II or III exposures receive RIG and 1-site IM on days 0, 3, 7, 28			

Table 1.4 Rabies PEP recommendations in the Philippines. Adapted from National Rabies Control Program [73, 79, 83]

Administration of rabies vaccine programs is carried out at the local level. The DOH procures rabies vaccines which is distributed to regional health offices, then to provincial health offices, and finally to ABTCs. The DOH mandates that vaccine utilisation, schedule completion and adverse event data be reported quarterly to DOH. Additionally, the National Rabies Information System (NaRIS) was created for continuous and systematic data collection. The main feature of NaRIS is the web-based point-of-care patient data entry for ABTC use which collects data including demographics, rabies exposure history, vaccine type administered, and doses received. It was intended to have the capacity to perform vaccine inventory based on registering vaccines administered, however NaRIS use has been limited in ABTCs [79]. Based on regional reporting, the DOH estimates 1.1 million patients received PEP in 2018 [79]. Vaccine supply is an issue as there are recurrent global shortages of rabies vaccines, and counterfeit vaccines were reported between 2017 and 2019 in both private

clinics and a large tertiary hospital [117-119]. The secondary feature of NaRIS is the information portal which the public can access to acquire rabies information including ABTC locations. It can also be used to report rabies cases in their community.

1.5 Rabies Vaccine Uptake and Theoretical Models Framing Vaccine Decision Making

While rabies PEP is highly effective in preventing disease, there were an estimated 377 preventable deaths in the Philippines in 2019, indicating issues with vaccine uptake. There are currently limited published data on rabies PEP initiation and adherence in the Philippines. A study conducted in 2008 reported that only 54% of patients returned for their second dose, 44% for their third and 32% for their fourth [120]. A more recent study in 2018 across three provinces in the Philippines reported 78% of patients completed their vaccine series. However, this varied across locations, with some areas reporting completion rates of 60% [74]. It is therefore essential to explore the factors associated with, and the facilitators and barriers to vaccine uptake. A literature review of these factors associated with rabies vaccine uptake will be presented in Chapter 3. The original research exploring vaccine uptake at the study site is then presented in subsequent chapters.

To design the research studies in this PhD, theoretical models of vaccine uptake were reviewed to build a framework to guide study conceptualisation.

Researching rabies vaccine uptake is a unique challenge as a single established health behaviour change theory does not adequately represent its nuance. Improving initiation and adherence to rabies PEP requires a health behaviour change following exposure but prior to onset of symptoms. Most theoretical frameworks for adherence are often aimed at preventative care where no exposure has occurred (e.g. childhood immunizations or hygiene practices [121, 122]) or long-term therapies after symptoms have begun (e.g.

prescribed exercise, tuberculosis treatment or HIV antiretroviral therapy [123, 124]). Additionally, behaviour change theories for vaccine adherence often use the constructs of social responsibility whereas this is not applicable to rabies vaccine as it does not confer herd immunity.

Therefore, several behaviour change models were reviewed. This included general models of behaviour change in addition to those specific to determinants of vaccine uptake. The most relevant to rabies vaccine uptake were the Health Belief Model (HBM) [125], the WHO SAGE Working Group on Vaccine Hesitancy's "3 Cs" [126] and "vaccine hesitancy determinants matrix" [127], and Betsch's "determinants of vaccine decision making" [128].

Shown in Figure 1.2, the Health Belief Model's constructs of perceived susceptibility, perceived severity, perceived benefits, perceived barriers and cues to action have been the basis of vaccine uptake models [129, 130]. However this model does not capture vaccine hesitancy, currently key to understanding vaccine uptake in certain contexts [127]. The "3 Cs" model highlights three concepts that determine vaccine hesitancy; complacency, convenience and confidence [126]. The second SAGE model (Figure 1.3) groups factors such as vaccine knowledge, perception of the pharmaceutical industry, and costs into individual, contextual and vaccine-specific influences. Betsch's model (Figure 1.4) adapts the Health Belief Model to include modifying factors such as descriptive norms and personal identity. This is essential to understanding vaccine decision making as societal factors are a major influence on vaccine uptake. Constructs from these models guided development of data collection instruments and analysis plans, and these theoretical frameworks will be discussed in relation to study results later in this thesis.

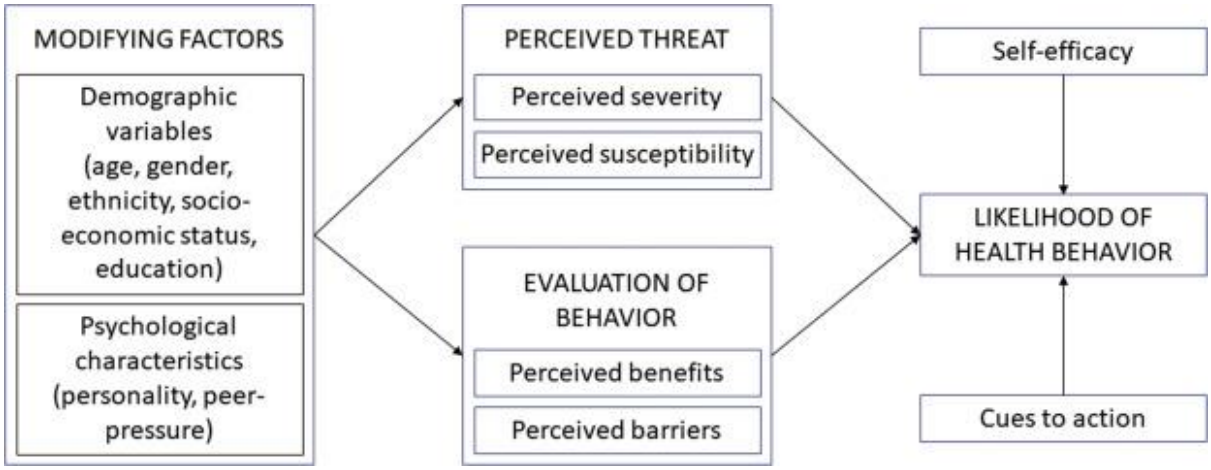


Figure 1.2 The Health Belief Model [125]

Figure 1.3 SAGE WG "model of determinants of vaccine hesitancy" [127]

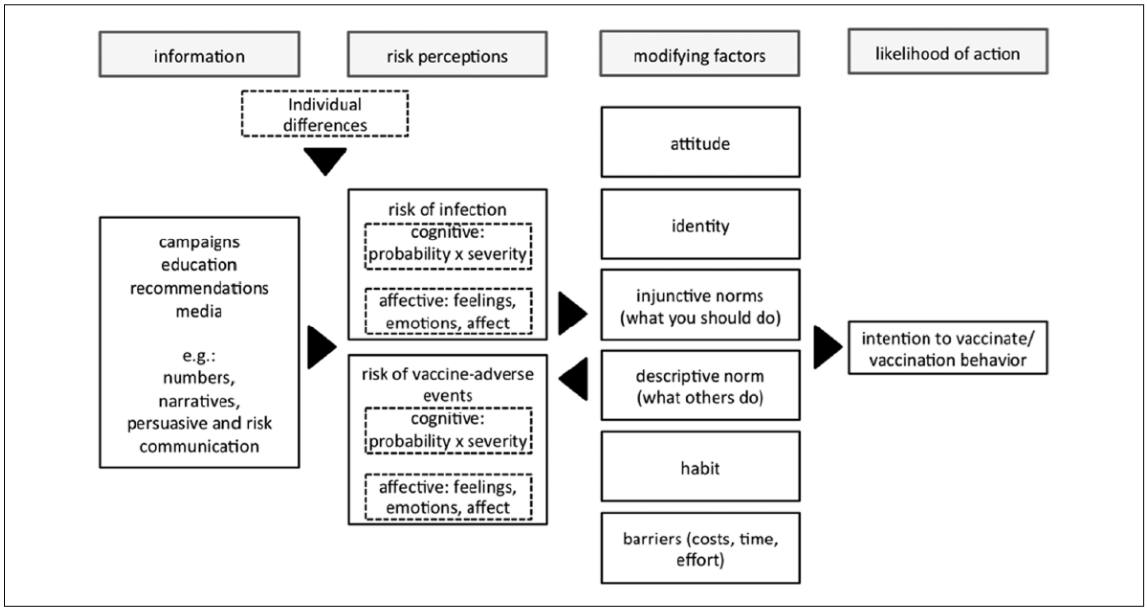


Figure 1.4 Betsch's "determinants of vaccine decision making" [128]

2 PhD Project Overview

2.1 PhD Rationale

Every rabies death is a traumatic experience for the dying patient, their family, and the medical staff. Due to the neurological impacts of the rabies virus, patients alternate between lucid and manic phases which are hard to manage and create a stressful medical environment. As the rabies vaccine is almost 100% effective, every rabies death is a preventable death.

Rabies is a disease of high consequence in the Philippines. The estimated 377 deaths a year is likely an underestimate. These deaths are due to rabies-exposed individuals failing to initiate or complete vaccination. There are limited data on the proportion of rabies PEP patients who complete their vaccination schedule and the factors that prevent or facilitate completion. Globally, cost is a factor which has hindered vaccine uptake. However, as the Philippines provides free PEP, the non-cost related barriers are important to investigate. Furthermore, as the current pandemic has illustrated, healthcare access may be limited during disease outbreaks as a result of movement restrictions, and potential hesitancy of visiting hospitals for fear of contracting diseases. How these restrictions affect rabies vaccine uptake and deaths in the Philippines has not been previously explored.

The findings from this PhD will contribute to filling this knowledge gap and inform the Philippines government's rabies programme, as well as other countries with comparable rabies programs.

2.2 Aim, Objectives and Hypotheses

Aim

The aim of this PhD was to further the understanding of rabies prevention strategies, vaccine uptake, and knowledge, attitudes and practices in the Philippines.

Objectives

The objectives of this PhD were to:

1. Explore patient experiences in animal bite treatment centres.
2. Characterise adherence to the rabies vaccine schedule and investigate knowledge, attitudes and practices.
3. Characterise and understand failure to initiate rabies vaccination.

Hypotheses

The working hypothesis of this PhD was that there are demographics, rabies exposure factors, or knowledge, attitudes and practices, which influence vaccine uptake. The quantitative studies have specific hypotheses detailed below.

Study 2 Hypothesis: The study was designed to test the null hypothesis that factors such as demographics and rabies exposure cannot predict vaccine adherence outcomes, and the alternative hypothesis that these factors can predict vaccine adherence outcomes with statistical significance.

Study 3 Hypothesis: The study was designed to test the null hypothesis that factors such as demographics, vaccine confidence, rabies exposure, and knowledge, attitudes and practices cannot predict vaccine adherence outcomes, and the alternative hypothesis that these factors can predict vaccine adherence outcomes with statistical significance.

Study 4 Hypothesis: The study was designed to test the null hypothesis that factors such as demographics, vaccine confidence, rabies exposure, and knowledge, attitudes and practices cannot predict vaccine initiation, and the alternative hypothesis that these factors can predict vaccine initiation with statistical significance.

2.3 Study Site

The Philippines has a population of 110 million. As illustrated in Image 2.1, it is divided into 17 regions, (population ranges from 1.7 - 15.4 million), 82 provinces, and 42,045 barangays (the smallest administrative division equivalent to a village). The 3 largest regions are Calabarzon (region 4A), the National Capital Region, and Central Luzon (region 3) with populations of 15.4, 13.5 and 11.9 million respectively [72].

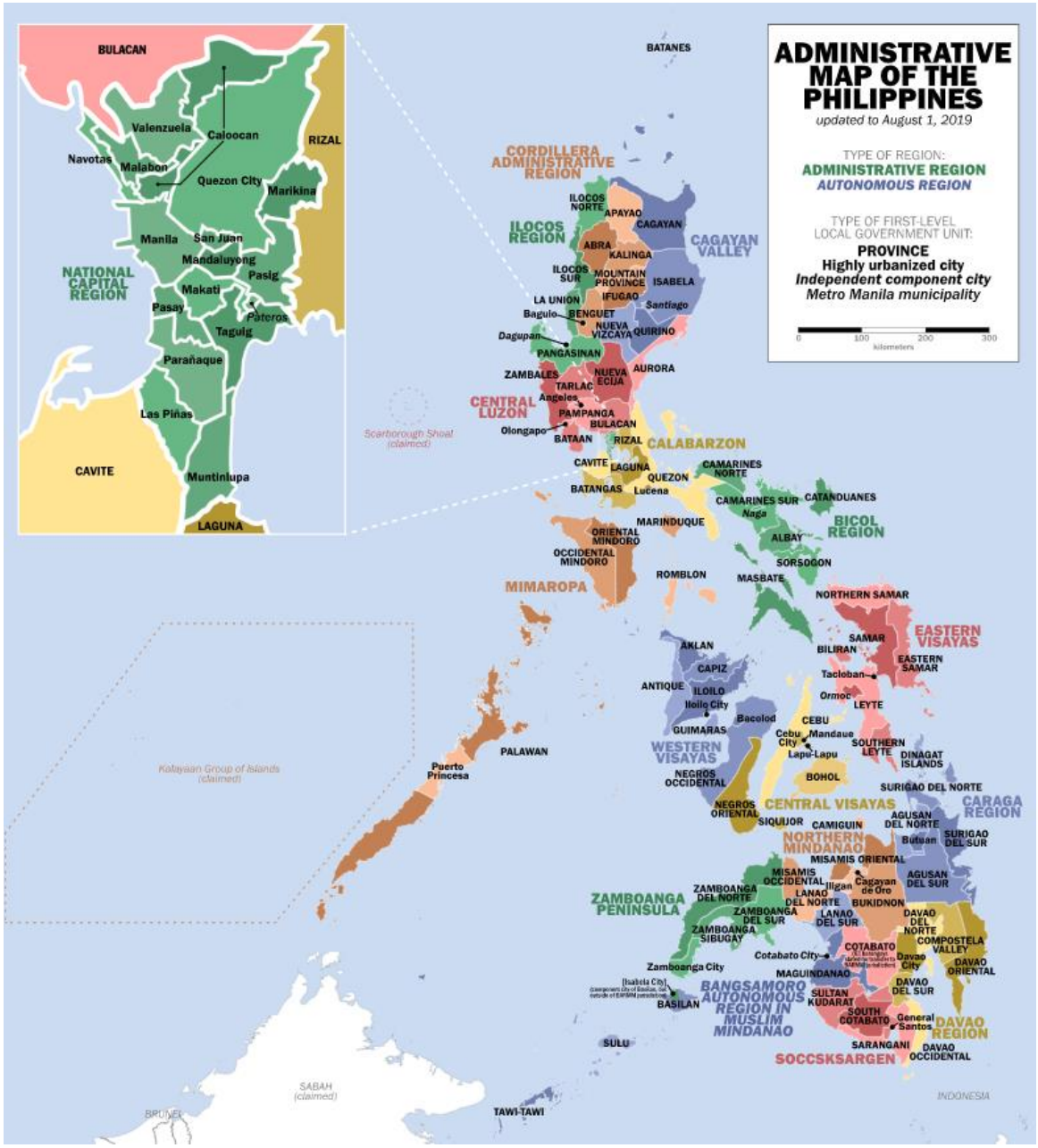


Image 2.1. Administrative map of the Philippines. Reproduced with courtesy: Isagani, 2019 [131]

This PhD research was conducted at San Lazaro Hospital (SLH). SLH is a tertiary referral health facility for infectious diseases located in Manila, National Capital Region. Rabies patients are transferred to SLH from across the National Capital Region, Central Luzon and Calabarzon. The ABTC, situated in the hospital's outpatient department, receives all rabies exposed cases which includes all animal contact cases except snake and insect bites which are taken to the emergency department. It receives the most animal bite patients across the Philippines, approximately 100,000 a year and up to 500 a day. The provinces with the highest rabies incidence rate in the country, Central Luzon and Calabarzon, are near Manila, this provides sufficient opportunity for participant recruitment of potential rabies exposed patients. The majority of patients seeking PEP at SLH reside in Manila or across the National Capital Region.

2.4 Ethics

Ethical approval was received from the London School of Hygiene & Tropical Medicine Research Ethics Committee (LSHTM Ethics Ref: 22718. 29/10/2021) and the San Lazaro Hospital Research Ethics Review Unit (SLH-RERU-2021-004-1) 21/01/2022).

2.5 Funding

This PhD research was funded by the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) through the WISE Program (Doctoral Program for World-leading Innovative & Smart Education) at Nagasaki University.

Extra stipend support was received from the LSHTM Scholarship team through the COVID-19 Extension Scheme.

2.6 Data Collection Timelines

Data were collected at San Lazaro Hospital between January to September 2022:

- Study 1: Healthcare provider interviews were carried out from January to February 2022.
- Study 2: Retrospective data from SLH databases was received in April 2022 (2016-2020 dataset) and September 2022 (2021 dataset).
- Study 3: Pilot tests were conducted in March 2022 and recruitment was carried out from March to May 2022. Follow up was carried out between April and July 2022.
- Study 4: Participants were enrolled in April and May 2022, although active recruitment was ongoing for the full duration of Study 3 from March to July 2022.

2.7 Unpursued Proposed Objectives

Two objectives were initially proposed but were left unpursued as it was not feasible to undertake them.

First, an objective to characterise national adherence to the rabies vaccine schedule across the Philippines using the data from the Department of Health's National Rabies Information System (NaRIS). NaRIS was created as a web-based system for point-of-care patient data entry into a database which is immediately accessible and available at the DOH. Approximately 4.5 million patients received PEP between 2010-2019 nationally [79]. This would have been a robust dataset. Data of patients who received first dose rabies vaccine were to be extracted, including these variables; age, sex, address, exposure category, animal type, vaccine administration (dates and dose number) and RIG administration (date and dosage). Similar to the SLH data in Study 2 (Chapter 5), this dataset would have been analysed to assess proportion of completion, and logistic regression analyses would have

been conducted to assess factors associated with vaccine adherence. Initial meetings with DOH were conducted however, it was not feasible to receive this national data. Furthermore, NaRIS use has been limited in ABTCs.

Secondly, an objective to investigate interventions to increase adherence to rabies vaccination schedules. This study proposed the use of focus groups to explore approaches to increase adherence. Potential interventions would have been designed using information from three sources; a) a literature review of PEP and vaccine (rabies and others) adherence interventions; b) data on barriers and facilitators derived from Study 3 and; c) consultation with SLH collaborators. Potential interventions may have included reminder messages, education on disease risk, provision of information in local languages, messages on vaccine stock availability etc. These would then have been presented in focus groups to examine potential benefits, usability, and saliency of the different approaches. The proposed focus groups would have comprised of participants recruited during Study 3 and additional participants enrolled in the community. Recruitment of non-Study 3 participants was to be carried out through flyers at SLH and other local clinics. Three to four focus groups of six to eight participants were to be conducted: one homogenous group of participants who did not complete vaccination, one heterogenous group of mixed vaccination status, and one or two groups of mixed vaccination status and participants recruited in the community who had not previously received rabies vaccine. The focus group guides would have been created in English, translated to Tagalog and back translated to English for quality control. The focus groups were to be audio-recorded, transcribed, translated, and analysed. Following the PhD qualifying exam, the number of objectives was considered overly ambitious by examiners, and it was suggested that this objective be dropped or kept on only as a potential study if feasible within time limits. Due to the COVID-19 pandemic's effect on research capacity at

SLH and travel restrictions which kept me from reaching the research site, data collection timelines were significantly delayed which prevented the potential development of interventions to be examined and therefore, this objective was not feasible.

2.8 COVID-19 Impact Statement

The lockdowns were strict in the Philippines, so severe, it was considered a human rights crisis by some [132]. Patients were unable to go to hospitals for non-COVID-19 related issues, therefore a reduced number of patients were receiving rabies vaccinations. Complete lockdown was in place from March – August 2020. Restrictions initially decreased in August, but measures were reintroduced, due to the delta variant, from November until summer 2021. San Lazaro Hospital is the referral site for infectious diseases and the main COVID-19 hospital. This redirected most work and research to COVID-19. Ethics applications for COVID-19 research were prioritised leading to ethical approval for the PhD to be severely delayed, and finally received in January 2022.

The inability to travel to the Philippines between March 2020 and April 2022 slowed down research processes and project management, and significantly delayed data collection. Due to the time difference between the UK and the Philippines, and the use of physical paper systems, research processes took more than double the expected times than if the researcher was in Manila. Primary data collection and receipt of secondary data was delayed by 18 months in comparison to the initial timeline. These issues led to delayed participant recruitment which substantially impacted Study 4, necessitated dropping of the proposed intervention study described in section 2.7, and led to other changes in the planned research rollout.

Steps were taken to mitigate these issues including the use of video conferencing for healthcare provider interviews as opposed to the initial face-to-face plan, and an onsite research assistant was hired to begin enrolment before the researcher was able to be physically present in the Philippines. However, there were significant delays in the research timeline.

There may be unmeasurable effects of the COVID-19 pandemic on study results. The number of patients accessing the ABTC reduced between 2019 and 2021, and while it increased in 2021, it was not back to pre-pandemic levels. As no observations were carried out during the height of the pandemic when lockdowns were in place in Metro Manila, it is difficult to assess the impact of restrictive measures. Post-lockdown, the only observed differences at the ABTC were face-shield and mask requirements, and a change in the waiting area for vaccination from indoors to outdoors.

2.9 Study Summaries

Study 1
Observational study of PEP procedures at the San Lazaro Hospital ABTC

Study 1 fulfilled objective 1 to explore patient experiences, provider practices, and vaccine recommendation in animal bite treatment centres (ABTCs). The study site was the ABTC of San Lazaro Hospital (SLH). Document reviews of vaccine guidelines and forms used during patient visits were carried out. Observation of patient-provider interactions were conducted in November 2019, January 2020 and May-July 2022. In-depth interviews with 10 providers were carried out to provide further context of ABTC procedures and explore provider perceptions of barriers to vaccine uptake.

Study 2
Retrospective Analysis of Vaccine Completion

Study 2 partially fulfilled objective 2 by characterising adherence to the rabies vaccine schedule. A retrospective analysis of 310,692 patients at SLH ABTC from 2016-2021 was conducted to describe the ABTC population and assess vaccine completion. Logistic regressions of independent variables age, gender, region of residence, and bite type, were conducted to assess factors associated with vaccine adherence.

Study 3
Prospective Study on Vaccine Uptake

Expanding on objective 2, this mixed method study used KAP surveys and interviews to assess vaccine adherence, immunisation attitudes, factors associated with adherence, and understand facilitators and barriers to vaccine uptake. 506 participants were enrolled at their first vaccine dose, Day 0. At Day 30+, participants received a follow-up call to self report vaccine completion. Data were analysed using logistic regressions to investigate

potential factors associated with vaccine completion. 17 participants were invited to partake in in-depth interviews which explored barriers and facilitators to vaccine uptake.

Study 4

Cross-sectional Study to Characterise Failure to Initiate Vaccination

Study 4 aimed to fulfil objective 3, using a cross-sectional study to characterise failure to initiate vaccination. Snowball sampling was used to recruit participants for Study 4. Snowball sampling is the research sampling method based on a referral system wherein participants are asked to recommend potential study participants that fit the research criteria, who then recommend further potential participants. Study 3 participants were asked to refer their contacts who had a potential rabies exposure but did not seek PEP. However, the sample size target was not met as only three participants were enrolled.

3 Literature Review on the Factors Associated with Rabies Vaccine Uptake

Introduction

Advances in rabies medical research have led to the development of a post-exposure prophylaxis (PEP) regimen consisting of wound management, and the use of passive and active immunisation. When administered timely and correctly, post-exposure prophylaxis is highly effective [20, 95]. Due to the high fatality rate of rabies, placebo-controlled vaccine efficacy trials have been considered unethical since the beginning of vaccine development. Therefore, there are no accurate statistics on clinical efficacy of current vaccines [20]. However, through animal models [133], immune correlates [89], comparative trials [134, 135], post-licensure surveillance [136], and reviews of vaccine failure rates in widespread use [109], the WHO has established that rabies post-exposure prophylaxis is almost 100% effective.

Despite this high vaccine effectiveness, there are still an estimated 59,000 preventable rabies deaths globally due to issues in rabies vaccine access and uptake. Access to rabies PEP is often affected by disease awareness, accessibility to medical centres, in-country vaccine shortages, and cost [137]. It is difficult to estimate vaccine initiation as animal bites and other potential rabies exposures often go unreported.

The Philippines aimed to mitigate these issues by education campaigns and increased access to vaccines. In 2016, the Philippines Department of Health (DOH) begun provision of free rabies vaccines and subsidised rabies immunoglobulin (RIG) [78]. Rabies vaccine was originally administered intramuscularly; however studies have shown that intradermal administration using multiple administration sites requires a lower vaccine volume while

proving as immunogenic as intramuscular administration [138-140]. The DOH shifted to the use of intradermal administration, recommended by the WHO, which reduces the cost to the government [79]. Consequently, vaccine shortages and stockouts can be decreased. Animal bite treatment centres (ABTCs) have also been established with a target of 1 ABTC per 100,000 people by 2030 [73, 78, 141]. However, issues around vaccine initiation and adherence persist. There are limited data on rabies PEP initiation and adherence in the Philippines. A study conducted in 2008 reported that only 54% of patients returned for their second dose, 44% for their third and 32% for their fourth [120]. However, these coverage data are likely to be an underestimate as patients may have received follow-up doses from a different health centre which would not be recorded in the system. Furthermore, as rabies vaccine has been provided free to patients since 2016, these data are outdated. A 2018 study across three provinces in the Philippines showed 78% of patients completed their vaccine series [74], 12% short of the 90% completion rate targeted by the Department of Health (DOH) [73]. However, this ranged across areas, with some barangays (village equivalents) reporting completion rates of 60%. To address adherence, the DOH developed and distributed rabies information leaflets to ABTC and encouraged healthcare providers to increase patient education on rabies risk and the importance of vaccination.

This literature review was conducted to provide an in-depth understanding of the issues surrounding rabies vaccine uptake globally by assessing the scope of available research and summarising the body of literature. It answers key questions such as - what are the barriers and facilitators to rabies vaccine initiation and adherence? Does hesitancy play a part? Do cultural contexts affect vaccine uptake in these studies? What studies have been conducted in the Philippines? Are studies underpinned by theoretical models or conceptual frameworks?

Methods

The literature review was conducted as a scoping review to summarise evidence on rabies vaccine uptake in individuals with a potential rabies exposure. A "potential" rabies exposure was used as the criteria for this review. This ensured the inclusion of both suspected and confirmed cases of rabies exposure, which is essential as according to WHO recommendations both categories require PEP.

The outcome of interest was the initiation of, or adherence to, the rabies vaccine schedule. Therefore, the comparator groups in quantitative studies were those that did not receive a full course of rabies vaccination.

Studies eligible for inclusion were both quantitative studies aimed at assessing factors associated with vaccine initiation and adherence, and qualitative studies exploring facilitators or barriers to vaccine uptake. This included prospective longitudinal studies, retrospective database analyses, retrospective surveys, cross-sectional studies, interviews, and focus groups. In papers where cross-sectional studies were conducted at ABTCs, this study design would only be capable of identifying factors associated with vaccine adherence, as the population accessing the ABTC would not be representative of vaccine-seeking behaviour by the wider population, and therefore vaccine initiation could not be explored.

The search strategy was developed with advice and input from an expert librarian at the London School of Hygiene & Tropical Medicine. The search was conducted across PubMed and Web of Science databases using key terms related to: rabies, vaccine, post-exposure prophylaxis, uptake, adherence, initiation, completion. The search terms were combined using open search strategies and the use of Boolean operators. Search terms were "rabies

AND (vaccin* OR post-exposure prophylaxis) AND (uptake OR adherence OR initiation OR compliance OR completion)". The expanded search strategy is in Appendix 10.1.

Study selection was conducted using the following inclusion and exclusion criteria.

Inclusion criteria:

- Studies on individuals with a potential rabies exposure.
- Studies located in countries categorised as endemic or sporadic transmission [142].

Exclusion criteria:

- Studies on pre-exposure prophylaxis.
- Studies centred on veterinarians, healthcare workers, or staff members in a hospital or vaccination centre.
- Studies in countries with no canine rabies [142].

1,249 studies were identified using the described search strategy. 252 of which were duplicates and 938 were excluded based on the title and abstract. 59 articles were fully assessed and 28 included in the final review. The steps from screening to inclusion are shown in the flow chart in Figure 3.1.

Of the articles that were fully assessed, one article was classified as "incorrect publication type" as it was an opinion piece which did not present new evidence-based information. Articles excluded for incorrect study design were cross-sectional studies at ABTCs investigating vaccine initiation or interventional studies that did report baseline reasons for initiation or adherence. Articles excluded for the incorrect outcome were generally studies that investigated population knowledge of rabies, evaluation of PEP dispensing procedures, or factors associated with rabies disease as opposed to vaccine uptake. Three studies had the correct study design and outcome, however there were no statistically significant associations reported.

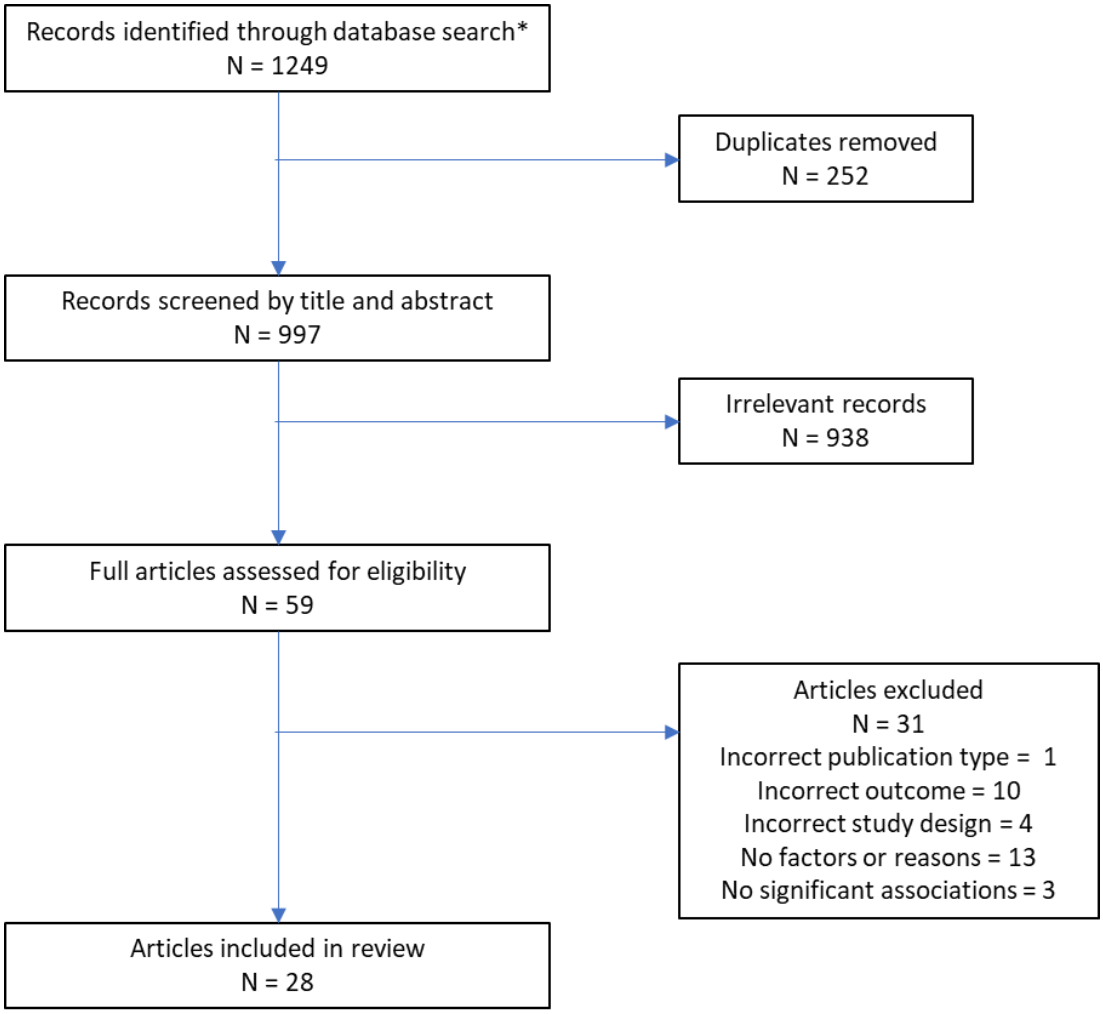


Figure 3.1 Flowchart of the literature review method from initial search to article inclusion

A descriptive narrative synthesis approach to reviewing results was used. This method was chosen because the scoping review was conducted to collate and understand the current body of literature, which provides a knowledge base for which the forthcoming PhD studies can build on.

Data extracted from articles summarised the geographical areas where studies were conducted, the proportion of vaccine initiation and adherence, and the factors associated with and the barriers to vaccine uptake.

Results

The review included 21 studies on adherence, and 7 which featured both initiation and adherence. The earliest study included was published in 2008, showing issues related to vaccine uptake have been studied for over a decade. Studies in 15 countries were identified; 7 in India, the most conducted in one country, followed by 4 in Côte d'Ivoire. Rabies vaccine adherence ranged from 1% in a study in India [143] to 94% in Bangladesh [144], with a median of 66%.

The studies included in this literature review are shown in Table 3.1 and summarised below:

One study in the Philippines was included. In this 2018 study across three provinces in the Philippines, potential exposures in the community were identified and 1,111 participants were enrolled. 45% of rabies-exposed participants sought care. The nonexclusive reasons stated for not seeking care after an animal bite were; study participants did not realise they needed PEP (37%), perceived high costs (23%), the wound was not severe (20%), the treatment centre was too far away (6%), belief in tandok i.e. traditional healers (6%), not knowing the location of treatment centres (4%), and the treatment centre was too busy (3%). 10% listed other reasons which included the dog being vaccinated, a belief in home remedies, and a decision that there was no rabies risk, amongst others. Of those who did not seek care at an ABTC, 50% practiced some home remedies ranging from wound washing, applying herbal salves, or bleeding the wound; and 30% visited a tandok. This study also recruited 1,105 ABTC patients, 78% of whom completed vaccination. It explored the reasons for incomplete PEP with the most commonly cited reasons being forgotten schedules, lack of money, belief vaccine wasn't needed, and no time, which were reported by up to 53%, 38%, 38% and 35% patients respectively in certain ABTCs [74].

Seven studies conducted in India were identified. One study reported 89% vaccine initiation, using a small sample size of 54 people. Vaccine completion ranged from 1% in rural Maharashtra to 79% in a cross-country study conducted in six states. Three studies reported intradermal administration as a statistically significant association to vaccine completion, while one study reported patients aged 60 and over were more likely to complete vaccination. Reported barriers to vaccine uptake included distance, cost, fear of loss of wages, forgotten dates, ill advice from friends or family, vaccine stockouts, busy schedules, and other logistical constraints. [143, 145-151]

Four studies conducted in Côte d'Ivoire reported adherence rates ranging from 53% to 65%. Zamina et al reported lower odds of incomplete vaccination when patients had knowledge of agitation as symptom aOR = 0.4 [95% CI 0.2–0.9] and higher odds of incomplete vaccination when patients had knowledge of animal bites as a mode of transmission aOR = 8.5 [95% CI 1.002–72.9] [152]. Tiembre et al reported 53% vaccine completion in 2009. Living outside the capital Abidjan, being unemployed, a Category II exposure (in comparison to III), the biting animal being alive and vaccinated were statistically significantly associated with incomplete vaccination [153]. A follow-up study also conducted by Tiembre et al in 2013 reported 57% completion. The reasons stated by participants for incomplete vaccination included – the animal owner didn't take responsibility 38%, costs 26%, didn't know they had to complete 10%, veterinarian certified the animal was rabies free 12%, a lack of time or transport 9% and other reasons 15% [154]. N'Guessan et al reported 57% completion. The 26-29 age group had higher odds of incomplete vaccination in comparison to reference age 0-10 (OR 67.9) and those resident in rural areas had higher odds of incomplete (OR 2.8). Participants in rural areas reported the major barrier to vaccine adherence was the distance of the clinic to their homes [155].

Two studies were conducted in China. One study reported 78% completion and focused solely on route of administration reporting a higher completion of 4-dose Zagreb schedule versus the 5-dose Essen schedule [156]. Guo et al reported 12% initiation and the following factors associated with failure to initiate vaccination: male aOR = 1.3 [95% CI 1.1–1.4], farmer occupation aOR = 1.4 [95% CI 1.1–1.8], age group "≥55" aOR = 1.5 [95% CI 1.1–2.2]. Adherence to vaccine schedule was reported at 20%, and the reasons for incomplete vaccination were: 70% developed rabies symptoms, 7%, believed vaccines were unnecessary, 2% cited costs, 2% had adverse reactions, and 1 case (0.2%) where the doctor did not think the individual needed to complete the series [157].

A study in Bhutan reported adherence of 83%, with higher odds of completion in urban areas OR = 2.7. Initiation was lower in males OR = 0.4 and educated persons OR = 0.4. The most frequently reported reason for lack of initiation was individuals who assumed risk of infection was minor if they were bitten by an owned or vaccinated dog [158].

The highest vaccine adherence in this literature review, 94%, was reported in Bangladesh. Of those who did not complete, 43% thought they did not need the full vaccine series for protection, 12% were too busy, 10% cited cost, 5% did not consider their wound a real bite i.e. injury was not perceived as a severe exposure [144].

A study in Brazil reported 66% vaccine completion. Demographic factors were investigated but none showed statistically significant associations. Patients who did not complete vaccination reported these reasons for noncompletion: thought additional vaccines were unnecessary 25%, inadequate understanding of the vaccination process 14%, and a lack of time 11% [159].

A study in Cambodia assessed factors associated with noncompletion which were: long distances from the vaccination centre, being male, aged 15-49 years, initial visit during rice harvest season, and a prescribed PEP protocol with more than 3 visits [160].

In Vietnam, a statistically significant association between patients bitten by a sick or rabid dog, compared to a healthy dog, and vaccination completion was identified; aOR = 3.0 (95% CI 2.6-3.4). There were no further statistically significant associations identified, however certain patient groups had higher vaccine completion: females, aged <15 years, and residence in high-burden provinces amongst others. [161]

In Thailand, a 15% completion rate was reported in a study where the highest proportion of incomplete vaccination was in patients who were: male, aged 16-45 years, received RIG, or received an IM regimen. However the associations were not statistically significant except for the route of administration. [162]

A study conducted in a large Peruvian city, Arequipa, investigated initiation and adherence in urban and peri-urban areas through focus groups composed of community members with a history of rabies exposure. Initiation was higher in urban areas versus peri-urban areas. In those who did not initiate or complete vaccination the reasons given were – 1) Painful vaccine - rabies vaccine had a reputation for being particularly painful. 2) A community perception that multiple vaccines could be harmful. 3) Thought one or two vaccines was enough. Some stopped PEP if the wound was healed. 4) Not completing because not treated well at health facilities or by health personnel 5) Lack of information about the importance of completion. 6) Lack of time. Urban residents emphasized 1-3 while 4-6 were most common responses for those residing in peri-urban areas. [163]

A prospective study conducted in an ABTC in Chad reported 88% vaccine completion with a 1.3 [95% CI 1.10-1.55] increased odds of incomplete vaccination in residents of rural areas. The main reasons reported for nonadherence were; the animal was not suspected to have rabies, the vaccine was not available at the ABTC upon return for follow-up doses, and the injury was not severe [164].

A cross-sectional study across three districts in Ethiopia was conducted to assess adherence and initiation through case investigations of ABTC patients and their contacts that did not initiate PEP, respectively. The sample size of 655 people showed 77% of those who had animal bites initiated rabies vaccination, and 57% of those who initiated completed the vaccine schedule. The factors associated with initiation and adherence were the animal of exposure being of an unknown owner, a severe injury, and living in an urban area. In addition, living closer to the ABTC and having a higher monthly expenditure, which was considered as a proxy for income and socioeconomic status, were further factors associated with adherence [165].

In Liberia, a retrospective analysis of an ABTC database reported 9% vaccine adherence. Residing in a rural area and being bitten on a lower limb were statistically significantly associated with a lower odds of vaccine completion.

A retrospective analysis of ABTC patients in Malaysia reported 81% vaccine adherence. People of Siamese ethnicity had higher odds of incomplete vaccination compared to those of Chinese or other ethnicities [166]. The authors suggest that nonadherence in the Siamese ethnic minority group may be due to two reasons. Firstly, people of Siamese ethnicity may have lower rabies knowledge and awareness as rabies health education material is available solely in Malay and English. Secondly, this study was conducted in Perlis state which borders

Thailand. As many individuals in the Siamese ethnic group hold Thai passports, it is possible that the population is more transient leading to vaccine completion outside Perlis state which is not recorded in this retrospective database analysis [166]. While these are potential factors, it is hard to make conclusive claims without a prospective study which investigates the issues leading to poor vaccine adherence in these communities.

A prospective study in Senegal reported 55% vaccine completion at an ABTC. Higher education levels and the receipt of rabies immunoglobulin was associated with higher odds of vaccine completion. Participants reported cost, not feeling ill, no availability to visit the ABTC, not understanding completion was necessary, and adverse events as the reasons they did not complete vaccination [167].

Two studies conducted in Tanzania were identified. A retrospective analysis of ABTC patients reported 46% vaccine completion. Adherence was statistically significantly higher in patients aged 15 and under compared to over 15, and in male patients. Patients that accessed the ABTC in rainy season, versus the dry, had lower odds of adherence [168]. A cross-sectional study of ABTC patients, and their contacts who did not initiate vaccination, reported 65% vaccine initiation in individuals with a potential rabies exposure. Some of the reasons reported for not initiating vaccination were the inability to afford treatment, vaccine stockouts at hospitals, a small wound, the owner of the biting dog did not provide financial support, and being unaware of the danger of rabies [169].

Discussion

Key Findings

In the quantitative studies, living in a rural area, in comparison to urban areas, was the demographic factor most frequently reported as a statistically significant association to poor

vaccine completion [155, 164, 165, 170], and failure to initiate vaccination [158, 163, 165], with four and three studies respectively.

Four studies reported gender as factors associated with vaccine uptake. Two studies reported male individuals were associated with failure to initiate vaccination [157, 158]. Regarding vaccine adherence, there were contrasting reports as one study each reported male [160] and female [168] individuals were statistically significantly associated with lower odds of vaccine adherence.

Sixteen studies reported barriers to vaccine uptake. The most common reasons for poor vaccine adherence were a lack of time in eight studies, thought further vaccine doses were unnecessary in seven studies, cost in six studies, and forgotten dates in five studies. Loss of wages, healthy or living animal of exposure, distance to ABTC, perceived low severity of injury, and inadequate understanding of the vaccination process were reported in four studies. While adverse events were reported in two studies [157, 167], the effect on uptake is likely minimal as percentages were 2% and lower.

Eight studies focused on the route of administration and vaccine schedule, the most commonly investigated independent variable. All studies reported a higher rate of vaccine completion when patients were administered vaccines in a schedule with lower number of visits, and a statistically significant association between intradermal (ID) vaccination and completion, in comparison to intramuscular (IM) administration of vaccines. These studies are important because they demonstrate that lower costs, and time saved and reduced inconvenience from fewer clinic visits, are likely the mediating factor related to increased vaccine adherence seen in ID administration. However, ID administration, recommended by

the WHO, is the standard of care in the Philippines, therefore these studies are less relevant to the context of the PhD studies.

All but one of the published papers were of quantitative studies. Therefore facilitators to vaccine uptake were not reported as this would be a theme more likely to arise in interviews or focus groups. Additionally, there was a limit to exploring barriers based on surveys.

The studies included in the literature review did not highlight theoretical models of vaccine uptake used to design studies or frame outcomes. This absence may signify that studies were not grounded in theoretical frameworks which could lead to gaps in the information that was derived from the study populations.

Patient Survival Following Rabies PEP

Rabies PEP is highly effective, however deaths in patients who received PEP have been reported [171]. These are generally linked to deviations from recommendations including the lack of, or improper administration of RIG in severe category III exposures, and are therefore not considered true vaccine failures [20, 109, 110]. Rabies cases that present with a history of appropriate wound management, RIG and vaccination are rare but have been documented. These cases often received multiple bites on the face and upper body [111-113].

The studies identified in this literature review were primarily focused on assessing factors associated with, and the barriers and facilitators to vaccine uptake. However, rabies mortality was reported in some studies.

A study in Tanzania identified 1,080 rabies exposed individuals from 2002 to 2006. Twenty-eight deaths from suspected rabies were reported [169]. Three of these patients had evidence of PEP. Two patients with severe injuries on the head, neck and spine (i.e. category

III exposure) began rabies vaccine regimens promptly but did not receive RIG. These patients developed rabies symptoms and died within 28 days of their exposure, before their vaccine schedule was complete. The third patient completed a four-vaccine series; however they did not receive RIG and the first dose was received on a delayed schedule, several days after the exposure.

A retrospective analysis of 10,771 animal bites at a hospital in Tanzania reported 46% vaccine adherence [168]. The study reported 48 suspected rabies deaths at the hospital during the study period of 2008-2014, however there was no data reported on the vaccination status of these patients.

A study in China investigated 10,971 rabies deaths between 2006 and 2012 [157]. Of the patients, 12% began PEP vaccination while 2% completed their vaccine schedule. However, only 0.4% received both RIG and a complete vaccination series as recommended.

A study in Vietnam investigated two rabies deaths in the study population of 14,296 rabies exposures [161]. 42% of all rabies exposures completed their vaccine schedule. Of the two deaths, the first patient did not complete vaccination. This patient was a 6-year-old who received ERIG and one vaccine dose. The second patient with a category III exposure was stated to have "(incorrectly) received ERIG and all four doses of vaccine on the same day of her exposure". It is unclear if this implies that the patient was administered an inappropriate vaccine schedule, receiving an excessive number of doses on the first day, and no follow up visits.

Of the studies that did not report rabies mortality, four studies explicitly stated that all participants were reached and alive, or that no rabies cases were reported during the study period [145] [165] [167] [74]. A majority of the studies did not have a hundred percent

follow up, and therefore the potential of participants being lost to follow up due to death from rabies cannot be excluded.

Delays To Vaccine Uptake

While this review focused on vaccine initiation and adherence, the timely uptake of PEP has an impact on rabies onset and survival. A study conducted in eight Asian countries including the Philippines showed that 63% of animal bite patients accessed the ABTC within the first day of the rabies exposure, and 75% within two days [172]. Other studies investigated the causes of delays over forty-eight hours including a study carried out in Iran which reported a delay greater than forty-eight hours in 7% of patients who sought PEP. The factors associated with delay were; being bitten by an animal other than a dog, and a shallow wound [173]. Delays of 36% were reported in one study in China and the groups associated with delay were those aged 15-44 years, hurt by a pet, or with some knowledge of rabies incubation periods [174]. In India, delays of greater than forty-eight hours were reported in 41% of participants [175]. These delays were associated with long distances from the vaccination centre, lower family income and older adults. The reasons stated for delays were work-related barriers, vaccination centres being closed on Sundays and national holidays, and unawareness about the need for timely PEP [175]. A study in Tanzania reported 25% of rabies exposed individuals started their vaccine course more than one week later. A distance greater than 10km and a lower socioeconomic status were both statistically significant predictors of delays in receiving PEP [169].

In summary, delays were most common when; individuals had a reduced risk perception as seen in being bitten by a pet or an animal not commonly associated with rabies, or a shallow

wound; individuals were logistically unable to access ABTCs due to finances and travel distance; and rabies knowledge and awareness was low.

Immunisation Attitudes in the Philippines

Some studies in this review highlighted that rabies knowledge can have an impact on PEP uptake. However, immunisation attitudes and the potential effects of vaccine confidence on vaccine uptake were not reported on or discussed, except for in Castillo-Neyra et al [163]. Focus groups conducted in Peru highlighted that the rabies vaccine had a particular reputation for being painful, and that there was a community perception that the multiple vaccines in the schedule could be harmful. Additionally, some pregnant women reported their uncertainty of the vaccine's safety for them as a reason they did not initiate vaccination. As Castillo-Neyra et al was the only focus group study, it is unclear if vaccine hesitancy and immunisation attitudes are not current key factors related to rabies vaccine uptake, or if the surveys were not adequately designed to capture this information. Therefore rabies vaccine confidence could be a factor left yet unexplored.

In relation to this PhD's aims, it is important to consider vaccine confidence in the Philippines, which has traditionally been high [176]. However, as with occurrences across the world such as the discredited link between autism and measles mumps and rubella vaccine (MMR), incidences of mistrust and misinformation have led to temporary drops in vaccine confidence in the Philippines [177]. Reduced vaccination rates have been reported on a few occasions; in 1994 due to fears of sterilization associated with the tetanus vaccine [177-179], and most recently, the dengue vaccine scare in November 2017 [180].

Following the dengue vaccine scare, the Vaccine Confidence Project (VCP) reported a significant drop in vaccine confidence in 2018, using their measurement of four indicators:

importance, safety, effectiveness, and compatibility with religious beliefs. Confidence in vaccine safety fell from 97.3% in 2015 to 65.2% in 2018 [176, 181]. These decreases in vaccine confidence were reflected in measles vaccination rates falling from 88% in 2014 to 55% in 2018 which led to measles outbreaks, peaking at 18,000 measles cases in 2018 compared to 2,400 in 2017 [180].

Based on findings in published literature, the Philippines has maintained high confidence in the rabies vaccine, which could be due to the post-exposure nature of vaccination. In a 2009 community study in Bohol, 74% of respondents stated a willingness to receive PEP. The most common response for a lack of willingness was no prior knowledge of PEP [182], which is not closely linked to vaccine hesitancy. A more recent community survey in 2018 did not uncover vaccine hesitancy except in the rare cases of pregnant women [74]. Although the public has generally held high confidence in the rabies vaccine, the DOH reports common myths and misunderstandings present in the community, including that the rabies vaccine injections are specifically very painful [73]. The DOH highlights this in its rabies prevention and control manual of procedures for doctors and program managers to tackle these misconceptions which may affect PEP uptake and adherence.

Rabies Education and Awareness

Rabies education and awareness is one of the components of the rabies prevention strategy developed by the WHO [95]. Studies have shown that education programs in schools and communities increase rabies awareness, including an improved understanding of what constitutes a rabies exposure, post-exposure wound management and vaccine schedules, and identification of human symptoms and clinical signs in animals [183-185]. A study in the

Philippines evaluated a program which integrated rabies education into school curriculums. The study reported reduced biting incidence in addition to increased rabies awareness [81].

In this literature review, some reasons reported for poor vaccine uptake are associated to low rabies knowledge, which could be modified with education. Examples of such reported reasons are i) unawareness of the danger of rabies, ii) unawareness of the necessity of vaccination, iii) misconception that small wounds do not lead to rabies, iv) misconception that a lack of ill health meant vaccines were unnecessary [74, 147, 167, 169, 186]. One study reported that patients who had knowledge of agitation as a clinical sign in animals, had reduced odds of nonadherence (aOR = 0.43 [95% CI 0.20–0.93]) [152].

Interventions to Improve Vaccine Uptake

The studies in this review have investigated the financial, logistical, knowledge, and attitudinal issues related to vaccine uptake. However, few have put forward evidence-based proposals to improve uptake. Two studies screened in the literature review trialled interventions. A study in Cote d'Ivoire utilised mobile phone reminders which resulted in an increase in completion from 41% (95% CI 37-44) to 55% (95% CI 52-59) [187]. A 2015 study in Haiti reported a 45% (95% CI 39-50) increase in initiation, and a 25% (95% CI 16-34) increase in adherence associated with integrated bite case management counselling [188].

Conclusion

In conclusion, studies across endemic countries have been conducted to understand rabies vaccine initiation and adherence. However, no published systematic reviews which reported on the factors associated with, or facilitators and barriers to vaccine uptake, both globally and specific to the Philippines, were identified. The body of literature identified in this scoping review points towards residence in rural areas, and animal status and ownership, as

main factors associated with vaccine uptake. These factors have been recognised by the WHO [189]. The WHO and OIE included both strengthening access to vaccines in rural areas, and increasing responsible pet ownership, in the 2016 report on the global elimination of dog-mediated human rabies [189]. In the studies included in this literature review, the most common reasons for poor vaccine adherence were a lack of time, costs, thinking vaccination was unnecessary or not understanding the need to finish the schedule, and forgotten dates. Overall, there are limited data in the context of the Philippines.

Table of Articles in Literature Review

Table 3.1 Articles included in literature review

Factors are associated with incomplete vaccination or failure to initiate except where stated that the inverse is presented. Where no OR is presented, factors were assessed as a statistically significant association using a chi-squared test (χ^2 p value <0.005). Where OR is presented without 95% CI, it was omitted in the paper.

	Year	Author	Study Type	Adherence/ Initiation	Period	Location	Study Population	N	Adherence/ Initiation %	Significant Factors OR (95% CI)	Reported Barriers	Ref
1.	2020	Alam AN	Prospective	Adherence	03/2013-07/2013	Bangladesh	ABTC patients	885	94%	/	•43% thought full protocol unnecessary •12% too busy •10% cost •5% injury not severe	[144]
2.	2019	Penjor K	Cross-sectional	Both	01/2017-06/2017	Bhutan	Case investigation of prior ABTC patients and contacts that didn't initiate PEP	483	Ad 83%	Completion OR Initiation •Male OR 0.4 •Educated OR 0.4 •Unprovoked bite OR 5 Adherence • Urban OR 2.7	•Assumed infection risk minor if bitten by owned or vaccinated dog	[158]
3.	2011	Veloso RD	Cross-sectional case series	Adherence	2006	Brazil, Port Alegre	ABTC patients	280	66%	No statistically significant association	•Thought unnecessary 25% •Inadequate understanding of vaccination processes 14% •Lack of time 11%	[159]
4.	2020	Madjadinan A	Prospective	Adherence	2016-2018	Chad	ABTC patients	1,297	88%	•Rural: OR 1.3, (1.10–1.55)	•Animal alive •Vaccine not available •Injury not severe	[164]

	Year	Author	Study Type	Adherence/ Initiation	Period	Location	Study Population	N	Adherence/ Initiation %	Significant Factors OR (95% CI)	Reported Barriers	Ref
5.	2018	Tarantola A	Retrospective	Adherence	2009-2013	Cambodia, Phnom Penh	ABTC patients	100,660	92%	•Further distances •Longer transportation times •Higher transportation costs •>2 day delay 1.1 (1.1-1.2) •Age 15–49 (vs <15) 1.2 (1.1-1.3) •Female 0.9 (0.9-0.9) •Rice harvest season 1.2 (1.2-1.3) •Unhealthy dog 0.5 (0.4-0.6) •Animal killed 1.7 (1.4, 2.1) •Animal rabies confirmed 0.5 (0.4-0.6). •4 doses [vs 3] 4.1 (3.4-5.0) •5 doses [vs 3] 99.5 (79.9-123.9)	/	[160]
6.	2018	Guo C	Retrospective	Both	2006-2012	China	Rabies patient case investigation	10,971	Adherence-20% Initiation-12%	•Male aOR 1.3 (1.1-1.4) •Farmer occupation aOR 1.4 (1.1-1.8) •Age ≥55 aOR 1.48 (1.01-2.2)	•Developed rabies symptoms •Thought unnecessary 7% •Cost 2% •Adverse reaction 2% •Doctor recommendation 0.2%	[157]

	Year	Author	Study Type	Adherence/ Initiation	Period	Location	Study Population	N	Adherence/ Initiation %	Significant Factors OR (95% CI)	Reported Barriers	Ref
7.	2022	Zhang W	Retrospective case study	Adherence	01/2020-12/2020	China, Beijing	ABTC patients	2,095	78%	•5-dose schedule	/	[156]
8.	2019	Zamina BYG	Cross-sectional	Adherence	09/2014-05/2015	Côte d'Ivoire, Treichville	ABTC patients	744	/	• Knowledge of agitation as symptom aOR 0.4 (0.2-0.9) •Knowledge of transmission mode aOR 8.5 (1.0-72.9)	/	[152]
9.	2009	Tiembre I	Retrospective	Adherence	2002-2003	Cote d'Ivoire, Abidjan	ABTC patients	533	53%	•Resident outside Abidjan •Unemployed •Cat II •Animal alive •Animal vaccinated •5-dose schedule	/	[153]
10.	2013	Tiembre I	Prospective	Adherence	10/2009-01/2010	Cote d'Ivoire, Abidjan	ABTC patients	220	57%	•5-dose schedule	•Animal owner didn't take responsibility 38% •Cost 26% •Didn't know 10% •Vet stated animal rabies free 12% •No time/transport 9% •Other 15%	[154]
11.	2022	N'Guessan RD	Cross-sectional	Adherence	2017-2019	Cote d'Ivoire, San -Pedro	case investigation of prior ABTC patients	199	65%	•Age 26-29 [vs 0-10] OR 67.9 •Urban OR 0.4	•Distance to ABTC in rural areas	[155]

	Year	Author	Study Type	Adherence/ Initiation	Period	Location	Study Population	N	Adherence/ Initiation %	Significant Factors OR (95% CI)	Reported Barriers	Ref
12.	2018	Beyene TJ	Cross-sectional	Both	09/2013-08/2014	Ethiopia. 3 districts	Case investigation of prior ABTC patients and contacts that didn't initiate PEP	655	Adherence-57% Initiation-77%	Completion OR Initiation •Unknown dog owner aOR 2.6 •Severe injury aOR 2.2 •Rural residence aOR 0.1 Adherence •Unknown dog owner aOR 2.6 •Distance aOR 0.97 •Monthly spending >$100 [vs <20] aOR 2.5 •Rural aOR 0.06		[165]
13.	2019	Haradanhalli RS	Prospective	Adherence	05/2017-01/2018	India	ABTC patients	529	79%	•IM dose	•Loss of wages 32% •Forgotten dates 18% •Distance 14% •Negligence 9% •Cost 6% •Vaccine stockout 4% •Other 17%: interference with school timings, not properly advised	[145]
14.	2019	Ramesh Masthi NR	Cross-sectional	Both	07/2017/-11/2017	India	Household community survey	54	Ad 72% In 89%	/	Initiation • Thought unnecessary 83%	[147]

	Year	Author	Study Type	Adherence/ Initiation	Period	Location	Study Population	N	Adherence/ Initiation %	Significant Factors OR (95% CI)	Reported Barriers	Ref
15.	2015	Shankaraiah RH	Prospective	Adherence	01/2012-12/2012	India, Bangalore	ABTC patients	736	72%	•IM dose	•Loss of wages 43% •Forgotten dates 18% •Cost 14% •Distance 13% •Interferes with school 11%	[148]
16.	2014	Mankeshwar R	Retrospective	Adherence	2007-2009	India, Mumbai	ABTC patients	2,535	66%	Completion OR •ID dose 8.0 (6.6-9.6)	/	[146]
17.	2022	Panda M.	Prospective	Adherence	02/2019-07/2020	India, New Delhi	ABTC patients	360	48%	/	•Distance 50% •Fear of loss of wages 38% •Forgetfulness 28% •Ill advice from relatives/friends 21% •Animal observable 17% •Household responsibilities 8%	[151]
18.	2022	Pal R.	Prospective	Adherence	05/2020-04/2021	India, South	ABTC patients	122	74%	No statistically significant association	•Forgotten dates 34% •Lack of time 28% •Logistical constraints 6% •Other health issues 9% •Stopped by other physicians 22%	[150]
19.	2019	Gadapani B	Retrospective	Adherence	01/ 2017 - 12/2017	India. Maharashtra, Rural	ABTC patients	209	1%	•Age <60	/	[143]
20.	2017	Olarinmoye AO	Retrospective	Adherence	2010-2013	Liberia, Monrovia	ABTC patients	775	9%	•Rural residence •Lower limb bite site	/	[170]

	Year	Author	Study Type	Adherence/ Initiation	Period	Location	Study Population	N	Adherence/ Initiation %	Significant Factors OR (95% CI)	Reported Barriers	Ref
21.	2023	Basir MFM	Retrospective	Adherence	07/2015-06/2020	Malaysia, Perlis	ABTC patients	507	81%	•Siamese ethnicity vs Chinese/other aOR 2 (1.06-3.76)	/	[166]
22.	2020	Castillo-Neyra R.	Focus groups	Both	2016	Peru, Arequipa.	Community members	Ini - 254	/	Initiation: •Peri-urban residence [vs urban]	•Vaccine is painful. •Multiple vaccines could be harmful. •1 or 2 vaccines enough/ stop PEP when wound healed. •Not treated well at health facilities or by health personnel •Lack of information about the importance of completion •Lack of time	[163]
23.	2018	Amparo ACB	Cross-sectional & prospective	Both	02/2017-05/2017	Philippines	Household community survey & ABTC patients	2,216	Adherence-78% Initiation-45%	/	Initiation •Didn't know PEP necessary 37% •Cost 23% •Injury not severe 20% •ABTC too far 6% •Belief in tandok 6% •No knowledge of location of ABTC 4% •ABTC too busy 3% Adherence •Forgot schedule 53% •Cost 38% •Lack of time 35% •Thought unnecessary 38%	[74]

	Year	Author	Study Type	Adherence/ Initiation	Period	Location	Study Population	N	Adherence/ Initiation %	Significant Factors OR (95% CI)	Reported Barriers	Ref
24.	2019	Diallo MK	Prospective	Adherence	04/2013-03/2014	Senegal, Dakar	ABTC patients	840	55%	•Low education level aOR 1.6 (1.21) •No RIG at D0 aOR 3.3 (1.7-6.3)	•Cost 43% •Animal alive 31% •Did not feel ill 22% •Too busy 19% •Thought unnecessary 7% •Adverse event 2%	[167]
25.	2018	De Nardo P	Retrospective	Adherence	01/2008-12/2014	Tanzania, Dodoma	ABTC patients	10,771	46%	Completion OR •<15 [vs >15] 1.3 (1.2-1.4) •Rainy season 0.87 (0.81-0.93). •Male 1.16 (1.08-1.24)	/	[168]
26.	2008	Hampson K	Cross-sectional	Both	2002-2006	Tanzania. Rural	Case investigation of prior ABTC patients and contacts that didn't initiate PEP	1,080	Initiation-65%	/	•Cost •Vaccine stockout •Small wound •Dog owner did not pay •Unaware animal was rabid •Unaware of rabies danger •Medical staff did not advise PEP •Thought they received (records show tetanus)	[169]
27.	2020	Yurachai O	Retrospective	Adherence	01/2015-12/2015	Thailand, Eastern	ABTC patients	4,883	37%	•IM dose	/	[162]
28.	2019	Tran CH	Retrospective	Adherence	01/2014-12/2016	Vietnam	ABTC patients	14,296	42%	Completion aOR •Sick & suspected rabid 3.0 (2.6-3.4)	/	[161]

4 Study 1: Formative Study of PEP Procedures and Provider Perspectives at an ABTC

Research Paper Cover Sheet

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed <u>for each</u> research paper included within a thesis.

<u>SECTION A – Student Details</u>

Student ID Number	1807686	**Title**	Ms
First Name(s)	Oladeji		
Surname/Family Name	Oloko		
Thesis Title	Factors Associated with Vaccine Uptake: A Study on Rabies Post-Exposure Prophylaxis in The Philippines		
Primary Supervisor	Chris Smith		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

<u>SECTION B – Paper already published</u>

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

<u>SECTION C – Prepared for publication, but not yet published</u>

Where is the work intended to be published?	Health Education and Research

Please list the paper's authors in the intended authorship order:	Oladeji K Oloko, Pauline Paterson, Ana R Sayo, Ferdinand De Guzman, Chris Smith
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived and designed the study, drafted the interview guide, conducted all interviews, carried out analysis and drafted the manuscript. CS and PP provided feedback and guidance for study conceptualisation and analysis. All authors provided comments on the manuscript.

SECTION E

Student Signature	
Date	22/05/2023

Supervisor Signature	
Date	19/09/2023

Healthcare Providers' Perspectives on Rabies Vaccine Uptake in an Animal Bite Treatment Centre in the Philippines: A Qualitative Study

Abstract

Rabies is a fatal zoonotic infectious disease. Endemic to the Philippines, there are an estimated 377 deaths annually. This study aimed to explore patient experiences, provider practices, and vaccine recommendations in animal bite treatment centres (ABTCs) through a formative study at the San Lazaro Hospital ABTC.

Document reviews, patient-provider observation, and in-depth interviews with 10 providers were conducted. Patients spent an average of 2 hours at the ABTC. Total vaccine costs varied from ₱143 (£2.50) to ₱4,287 (£70) depending on if free vaccine was available and the route of administration. Intradermal vaccination required less vaccine volume and therefore resulted in lower costs than intramuscular vaccination. However, regardless of costs and economic status, social services offered financial coverage. The COVID-19 pandemic affected vaccine access and changed the ABTC functions. However, as no observations were carried out during the height of the pandemic in Metro Manila, it was difficult to assess the impact of restrictive measures. Post-lockdown, the only observed differences were face-shield and mask requirements, and a change in the waiting area for vaccination from indoors to outdoors.

Providers perceived the main cause of nonadherence was due to indirect costs, work commitments and fear of wage loss, travel outside Manila, and misunderstanding the importance of vaccine completion. Other reasons cited by providers as potential hindrances were the long lines and time-consuming procedures at the ABTC. Vaccine hesitancy and adverse events were not perceived to be key factors. Provider's perceptions of facilitators to

vaccine uptake were patient's preexisting knowledge of the severity of rabies disease, and the influence of patient's social networks.

Data derived from this study indicates that programmatic efforts to increase access to ABTCs outside Manila, streamlined processes at the ABTC, and increased education, may improve vaccine uptake.

Introduction

Rabies is a fatal zoonotic infectious disease which causes an estimated 59,000 deaths per year [13, 23]. Upon the onset of symptoms, there are no treatment options, but rabies is preventable by post-exposure prophylaxis (PEP). In the Philippines, rabies is endemic and there are an estimated 377 deaths annually [70]. However, this is likely an underestimate due to misdiagnosis and underreporting [59]. Additionally, there are approximately 1 million animal bites annually, and rising, indicating a higher risk of rabies than reflected by mortality rates [73]. Timely immunisation with an approved schedule of vaccines is almost 100% effective in disease prevention [36]. There are currently three vaccine schedule options for immunologically naïve individuals with a rabies exposure recommended by the World Health Organization (WHO). The schedules use an intradermal (ID) or intramuscular (IM) method of vaccine delivery in 3-4 visits over 7-28 days [89, 95].

In 2007, the Philippines Anti-Rabies act established prevention and control programs including canine vaccination, education campaigns and provision of human vaccines. The National Rabies Prevention and Control Program (NRPCP) aims to end dog-mediated rabies deaths by 2027 and achieve a rabies-free Philippines by 2030 [73]. In 2016, the Anti-Rabies Act was expanded by the NRPCP to provide free PEP and subsidized rabies immunoglobulin (RIG) across the country through the establishment of a decentralised network of animal

bite treatment centres (ABTCs) [85]. ABTCs primarily use the “Institut Pasteur Cambodia (IPC) 2-2-2-0-0” vaccine schedule (2-sites intradermal on days 0, 3 and 7; total duration 7 days). The Essen schedule is used for immunocompromised patient – “Essen 1-1-1-1-0” (1-site intramuscular [IM] on days 0, 3, 7 and 14; total duration 14 days) [95]. However, when non-WHO prequalified vaccine is used, an additional visit on day 28 is used for both schedules [73, 95]. Rabies immunoglobulin (RIG) is administered to some higher risk patients on day 0 or 3.

Although rabies vaccine is available freely across the Philippines there are still many preventable deaths. There are limited available data on PEP initiation and adherence. A study conducted in 2008 reported that only 54% of patients returned for their second dose, 44% for their third and 32% for their fourth [120]. Although, this coverage data is likely to be an underestimate as patients may have received follow-up doses from a different health centre which would not be recorded in the system. Furthermore, as PEP has been provided free since 2016, these data are outdated. A 2018 study across three provinces in the Philippines showed 78% of 1,105 patients completed their vaccine series [74], 12% short of the 90% completion rate targeted by DOH [73]. However, this ranged across areas, with some barangays (village equivalents) having completion rates of 60%. The main reasons stated for not completing the series were a lack of time to return to the ABTC, failure to remember when the next dose was due, and a lack of funds (for travel and other associated health centre charges) [74].

This study aims to understand healthcare provider perspectives of patient experiences at an ABTC to gain insights into the context of care, barriers that may lead to attrition, and interventions in place to increase vaccine uptake.

Methods

A formative study was conducted incorporating key elements of healthcare setting assessments. The study utilised data sources that included document reviews, observations of patient-provider interactions, informal conversations with healthcare providers and structured provider interviews.

Study Site: The study site, San Lazaro Hospital (SLH), is a tertiary referral health facility for infectious diseases located in Manila, National Capital Region (NCR). Rabies patients are transferred to SLH from across the NCR, and adjoining regions; Central Luzon and Calabarzon. The animal bite treatment centre (ABTC), situated in the hospital's outpatient department, administers rabies post-exposure prophylaxis.

Document Reviews: Program guidelines from the National Rabies Prevention and Control Program (NRPCP) and the Department of Health (DOH) were reviewed. Documents used at SLH during patient visits, including information leaflets, data collection forms, vaccine schedule reminders and payment slips were also reviewed. These documents provided an understanding of the guidelines, policies, and protocols in place for patient experience in ABTCs.

Observation of patient experiences and provider interactions: Observations were carried out in two phases. One week in November 2019 and January 2020 each, prior to the pandemic and over two months between May-July 2022. An estimated total of 150 patients were observed. Observation of specific patients along the pathway included a senior citizen, adult, minor, and a patient restarting vaccination schedule due to delay. Observational notes were written without personal identifiers.

Provider interviews: The provider interview guide was conceptualised following the initial period of observation. It was developed to understand the processes that patients undergo at the ABTC and how this may impact vaccine uptake. Questions sought provider perspectives on – vaccine refusal and hesitancy, frequency of stockouts, costs to patients, factors associated with adherence, information provided to patients during visits and other relevant patient-provider interactions. The interview guide was pilot tested and revised. Interviews with the providers at the ABTC were carried out from January to February 2022 via video conference by OKO. Participants were eligible if they worked at the ABTC, had patient interaction, and spoke English. Participants provided oral consent to ensure anonymity, as approved by the London School of Hygiene & Tropical Medicine and SLH ethics review committees. Participants were not provided financial compensation. Interviews were audio recorded, transcribed, and analysed in atlas.ti [190]. OKO has qualitative research and in-depth interview training, and experience conducting interviews and focus groups. A deductive thematic analysis approach was used for analysis. This method was selected as thematic analysis is the most practiced method to evaluate population opinions, knowledge, and experience [191]. Researcher OKO coded two transcripts, transcripts were read by PP & CS, codes were refined, and a codebook developed. OKO applied codes to all transcripts. Emerging themes were discussed by OKO, PP & CS. A guiding framework was then conceptualised as themes emerged and were categorised.

The study protocol was approved by the London School of Hygiene & Tropical Medicine (LSHTM) Research Ethics Committee (LSHTM Ethics Ref: 22718. 29/10/2021) and the San Lazaro Hospital Research Ethics Review Unit (SLH-RERU-2021-004-1) 21/01/2022).

Results

Document Review

The National Rabies Prevention and Control Program's 2019 Manual of Procedures is the guidance document providing direction on management and control of rabies including diagnosis, clinical management, surveillance, health communication, wound management, immunisation, and cold chain management. The Manual of Procedures informs operating procedures and protocols in ABTCs. All documents reviewed showed consistency in guidelines. At the time of the study, the following forms were used at the SLH ABTC. They are included in Appendix 0.

1. Patient's Hospital ID card – patient name and hospital ID
2. Patient Information Slip – filled in by patient and received by Records Department to create an electronic record in the integrated hospital management information system (iHOMIS).
3. Animal and Human Bite Data sheet, colloquially referred to as a "blotter sheet" – patient information and their assigned treatment plan.
4. PEP card – exposure history, vaccine type and schedule dates. This is kept by the patient as a schedule reminder.
5. Charge slip – issued by pharmacy, showing costs to be paid at cashier.
6. Prescription – issued by pharmacy, showing vaccine regimen to nurses.

These documents contained all necessary information for patients from entry to the ABTC to medical assessment, vaccine administration and exit. The PEP card, kept by the patient, listed doses and dates in a clear and understandable format.

Observation of Patient Experiences

Observations were carried out on 25-29 November 2019 and 13-18 January 2020 before the COVID-19 pandemic and 5-10 May 2022 and 13-14 July 2022 during the pandemic. Patient-provider interactions were observed by following the patient along the pathway, illustrated in Figure 4.1, from arrival at the ABTC and registration, to vaccine administration and discharge. This included periods of stationary observation at different sections, as well as following individual patients through the full pathway. Patients spent an average of 2 hours at the ABTC from registration to exit.

SLH ABTC receives vaccines from the DOH, termed "donations" by staff. When these vaccines were available, patients made no payments for the vaccine. At other times when not available, SLH purchased vaccines and patients paid for vaccines. The ABTC costs when vaccine was free were as follows: Outpatient Department ABTC registration – ₱50, rabies vaccine syringe – ₱8, tetanus toxoid – ₱55, tetanus syringe – ₱6, equine RIG (ERIG) – ₱2,000, human RIG (HRIG) – ₱6,000. Patients received HRIG if they had a reactive skin test to ERIG. Therefore, patients were observed to pay a total of ₱119 (£2), ₱2,119 (£32) or ₱6,119 (£94) for PEP without RIG, with ERIG or with HRIG respectively. When "donated" vaccine was not available, SLH purchased the vaccine and the cost to patients varied depending on the purchase price. The cost of a purified chick embryo cell (PCEC) rabies vaccine vial during July 8 to August 1, 2022, as observed on July 13 & 14 was ₱1,036 (£16). Each vial contained four intradermal doses so when patients identified a group of four and divided the costs, they paid ₱259 (£4) per dose in addition the previously described costs. However immunocompromised patients receive vaccine intramuscularly, requiring the full vaccine vial at each dose. As the purchased and "donated" vaccines may be different brands and composition, both purified chick embryo cell vaccine (PCECV) and purified Vero cell vaccine

(PVRV) were used during the observation periods, patients are maintained on the vaccine they begun. The pharmacy department ensures this by phasing in the purchased vaccine for new patients prior to the depletion of “donated” vaccine which is used for follow-up patients until the end of their vaccine schedule.

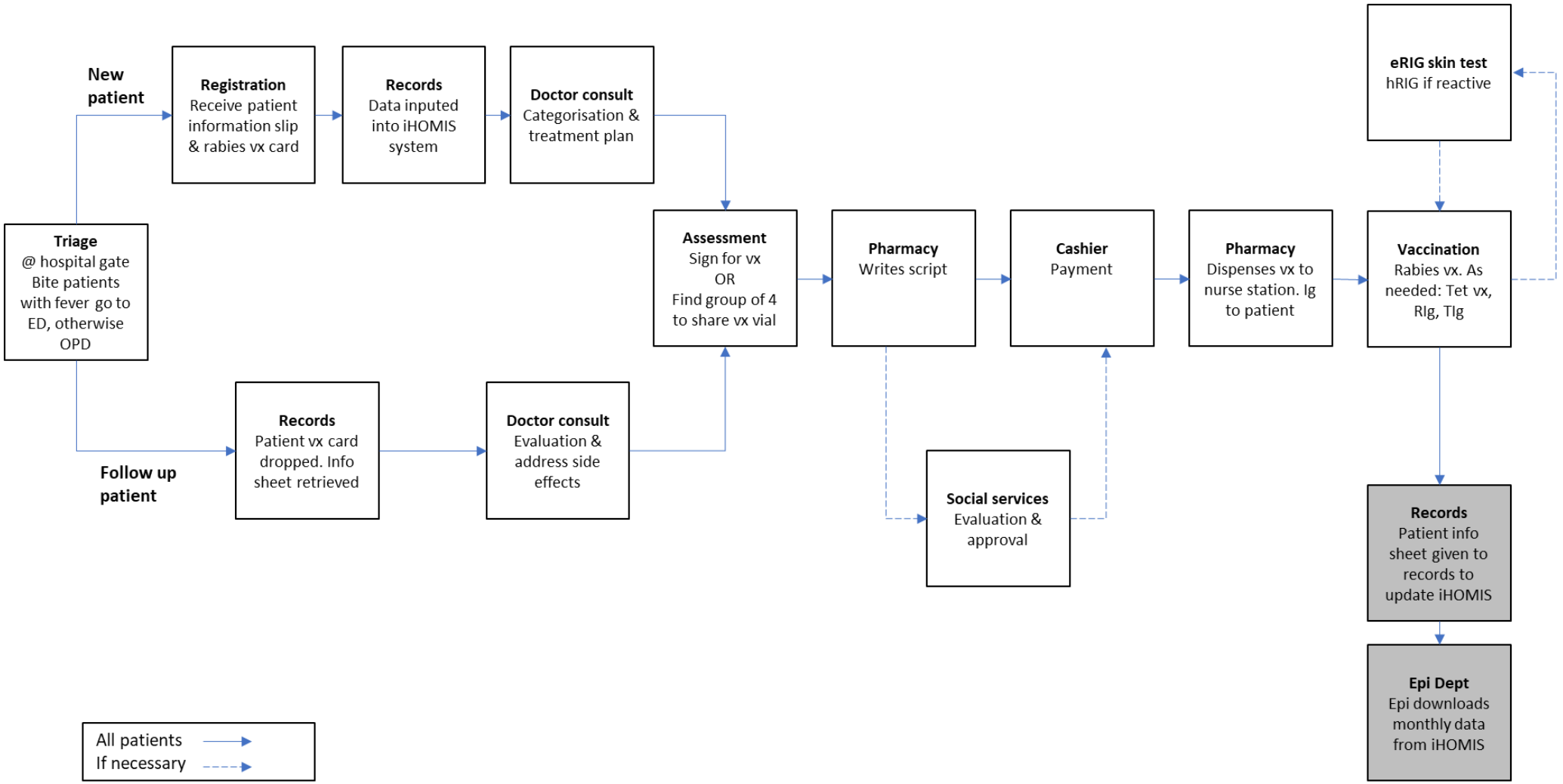


Figure 4.1 Patient flow through the San Lazaro Hospital ABTC as observed between 2020-2022. Grey boxes represent patient data flow

Provider Interviews

The target of interviewing providers in each role at the ABTC was met. Ten interviews were carried out: 3 doctors, 2 nurses, 2 medical records officers, 1 Medical Social officer, 1 nurse attendant and 1 pharmacist. Interview duration ranged from 14 to 44 minutes, lasting a median 23 minutes. Interviews with providers gave context to patient experiences, providers' perspectives on patient knowledge and behaviours, uncovered challenges providers face, and gave reasons for practices that differ from standard operating procedures. To protect anonymity of the providers interviewed, interview quotes will be labelled as healthcare worker (HCW1-10) except where the context of the position held is highly relevant to the information provided.

Provider Roles

Study participants were asked to describe their roles and the answers are summarised as follows. The doctors assessed patients' wounds, categorised the rabies exposures, and prescribed vaccination regimens. The nurses administered the vaccine, informed patients about the vaccine schedule, side effects, and the importance of completing the vaccination. The medical records officers created patient records by encoding demographic and medical data of the patients into the hospital database. The Medical Social officer provided guidance to access financial assistance and subsidy programs to cover costs of rabies immunoglobulin and vaccines. The nurse attendants provided patients with ABTC information and "*showed them where to go*". The pharmacists ensured proper storage of vaccines including monitoring daily fridge temperatures, and they dispensed vaccines and other medications such as antibiotics. Of the ten staff interviewed, four had worked at that ABTC less than a year, two for 1-5 years, two for 5-10 years and two for longer than 10 years. Of those who had worked at the ABTC for under a year, it was the first day for one staff member who had

been transferred from a different department of SLH but had prior training and experience working at the ABTC.

Providers stated a range of 350 to 1,100 patients visited the ABTC per day. Doctors, nurses, and the Medical Social officer stated they assessed, vaccinated, and assisted, respectively, approximately 100 patients each per day. The medical records officers stated they see about 400 patients each per day. While the pharmacist reported serving 150-300 patients per day. The amount of time patients spent at the ABTC from triage to exit, as illustrated in Figure 4.1, can be an important indicator of patient experience. Providers estimated patient visit duration ranged from 30 minutes to 4 hours, with 2 hours, stated by five providers, the most frequent response.

Vaccine Costs

Vaccines can be costly, especially when "donated" vaccines are unavailable. Patients unable to afford vaccines use the national health insurance scheme PhilHealth, or seek assistance from the Medical Social service called "Malasakit Centre", which enables them to have the vaccine costs covered. Therefore, providers believed that everyone who accessed the ABTC receives treatment regardless of cost, as the Medical Social officer stated –

> *"There is no minimum wage or whatsoever that we classify them … Everyone is welcome to have the financial assistance."* (HCW4)

Departure from International and National Guidelines

SLH procedures departed from WHO guidelines as four intradermal vaccine doses were used, instead of 3, and patients did not always receive RIG on the first visit. A provider explained that –

> *"We base on the animal status, if the animal is alive or dead… if the animal is a pet, there's a lesser chance that the animal has rabies… we keep the ERIG standby. But if on the follow up of the patient, the animal is dead or sick, that's*

the time that we add up the ERIG… and so far, nothing goes wrong… We consider category 3 if the animal is a stray animal and wounds that need to be sutured, the animal is sick, or any bite which is neck and above… That's the one that we do not avoid the ERIG and HRIG… But if the wound is on the hand and the animal is alive, according to WHO it's category 2, and we're supposed to give the ERIG or HRIG but we don't give that."[1]

Provider Perceptions of Factors Associated with Vaccine Uptake

The provider perceptions discussed below are conceptualised in a framework in Figure 4.2 which summarises the different factors that impact the intention to vaccinate, and the barriers and facilitators that mediate the final outcome of vaccination.

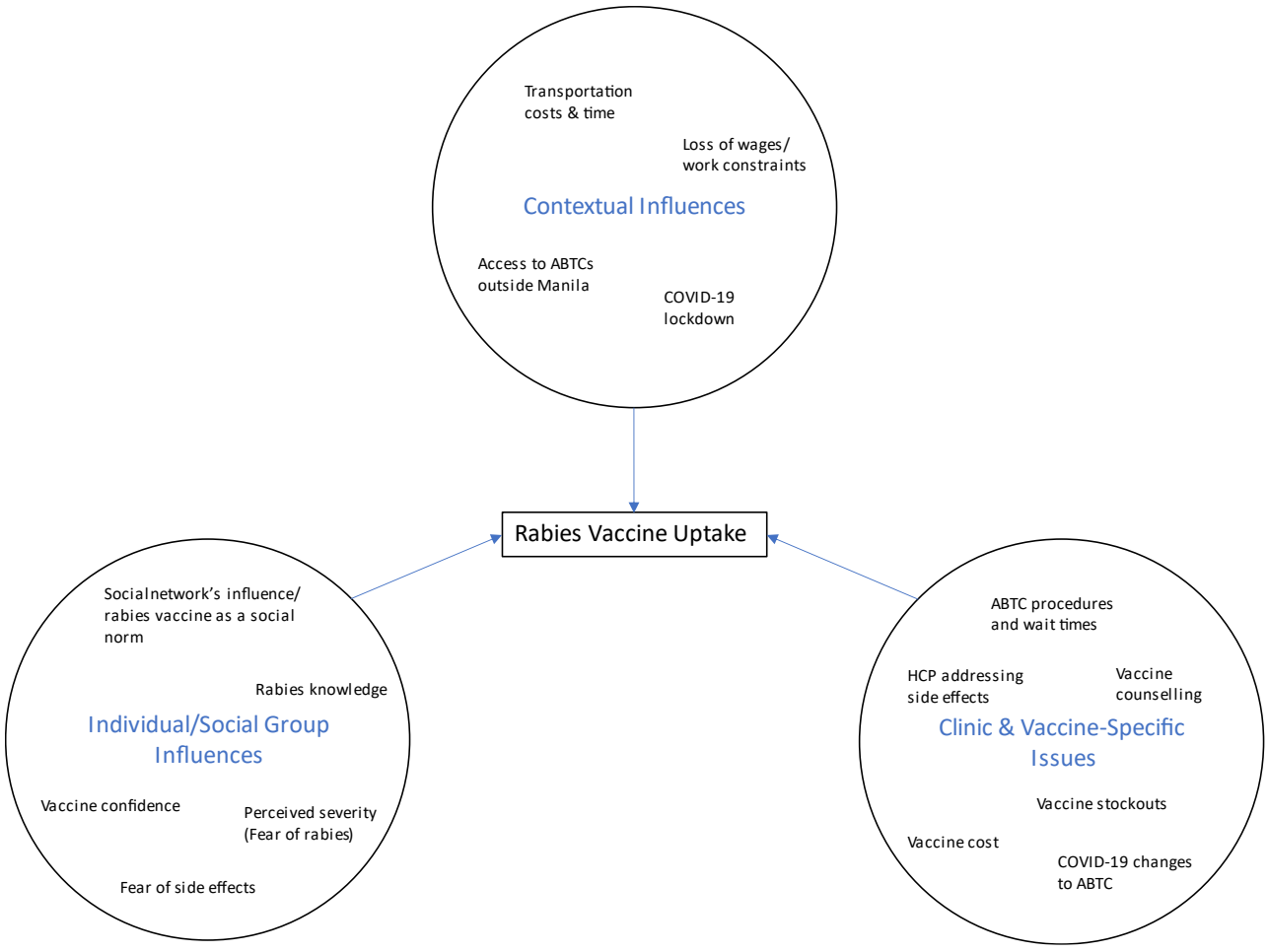


Figure 4.2 Conceptual framework of provider perspectives of the factors impacting rabies vaccine uptake.

[1] This provider described a wound on the hand as category II requiring RIG by WHO guidelines, however the WHO does not recommend RIG for category II exposures and categorises "single or multiple transdermal bites" as a category III exposure.

1. Vaccine Cost

Consensus amongst all providers was that all patients can receive vaccines as those unable to afford it are referred to the Medical Social office. The Medical Social officer supported this by explaining all patients receive support regardless of income –

> *"Because sometimes, even if you have money, there are times that we go through a hard time… So, we take that on consideration… We are required to help them 100%. There's no way that we cannot, we can't turn them down."* (HCW4)

2. Vaccine Stockouts

Majority of providers stated that stockouts are rare and therefore unlikely to impact patients' ability to complete doses. A provider who had been at the ABTC for 2 years had never witnessed a stockout, however, noted there have been RIG shortages –

> *"For PVRV [purified vero cell rabies vaccine], no. But with regards to HRIG we do run out of it."* (HCW2)

A provider who had worked at the ABTC for 8 years referenced stockouts of "donated" vaccine but reiterates vaccines are always available –

> *"On my experience there's out of stock and but not that long, so three days, then it's for free again. If there's no donation from DOH, we do have vaccines from our regular fund. We sell them to patients but if the patient can't afford that, we refer them to our Malasakit Centre".* (HCW9)

3. The COVID-19 Pandemic

On March 17, 2020, Manila went into enhanced community quarantine (ECQ), otherwise known as, lockdown [192, 193]. Public transport ceased and movement was prohibited except for procurement of essential supplies. All providers stated the reduced patient load, as described by this provider –

> *"The first part of the pandemic, patients rarely came because of the restrictions."* (HCW3)

One provider theorised that the reduced patient load may have also been due to less animal bites –

"…few patients came, maybe because there are a few people going outside so there are only few people who are bitten by a dog." (HCW4)

This provider then described the transition as Manila came out of lockdown with increased patient visits –

"…but after the lockdown and everything has been lifted, we had a lot of patients." (HCW4)

At the time of the interviews in January 2022, the ABTC was functioning as it did pre-pandemic with some modifications – mandatory use of face masks and shields, temperature checks at triage, and the use of outdoor holding areas. One provider described patient flow through the outdoor holding areas –

"…for the whole day, there's no [patient] limit, but for a certain period of time, for example, if for this hour, we only let 20 patients in and then after they're finished, the other 20 will come in. So no limit for the total number of patients but for the number of patients inside the OPD we impose a limit." (HCW8)

These modifications may have affected patient experience as providers stated that the outdoor holding areas are *"…making the process a little bit longer."* (HCW5). Additionally, privacy concerns arose as interviews for financial assistance which were conducted in private offices prior to the pandemic were now conducted outside. When asked if this became a privacy issue, the Medical Social officer stated –

"*Yes, because there are personal questions like their finances, work and everything, family background etc... But we make it assured that it is at least confidential, although there are some patients have listened. We just explain to them that it was the setting now. So, they have been able to understand the work setting that we had established because of COVID-19."* (HCW4)

These modifications described above, were employed to mitigate COVID-19 spread, however the possibility of patients feeling hesitant to visit hospital settings for fear of

contracting COVID-19 was considered. Five of the ten providers reported patients expressed fear and this could have potentially affected return visits. As one provider stated –

> *"There are some patients that are too afraid to go out and they just have their initial treatment and they'll be lost to follow up due to the scale of the pandemic, especially here in our institution where we cater to COVID patients as well."* (HCW8)

One of these providers described a more nuanced viewpoint believing that fear differed by socioeconomic class; that patients' prior encounters with difficult situations or preoccupation with more immediate concerns such as making a living, attenuated their fear, they described this as –

> *"It depends on the class. If it's class ABC. Yes, they are really afraid. For those who are in class C, D, or low-income class. I think they're more of a resilient spirit. They can go out, they laugh but they're really not aware of the effect of the COVID infection."* (HCW6)

The other five providers believed a majority of patients were not concerned evidenced by their attitudes at the ABTC –

> *"I don't think so. Because there are times that they get near with each other, they don't consider COVID."* (HCW7)

4. Vaccine Side Effects and Addressing Patient Concerns

Of the six providers that patients report side effects to, doctors, nurses and nurse attendants, all were in consensus that the most frequently reported side effects were minor: swelling, itchiness and rashes at the injection sites –

> *"Sometimes they'll tell [us] the injection site becomes swollen or itchy."* (HCW1)

Four of these providers believed that side effects were due to patients not following recommendations, commonly caused by consuming contraindicated foods –

> *"…we'll lecture them on the contraindicated food for rabies vaccine. Sometimes they forget then when they come back, they'll ask why was the*

injection site swollen. Then we reiterate what they should avoid. Then they remember what they took, what they ate to cause the swelling." (HCW1)

Of the six providers, five stated no experience with patients whose side effects may lead to hesitancy or a lack of adherence to subsequent doses. They believed they adequately counselled patients to ensure they understand these are mild, preventable side effects and they should not discontinue vaccination –

"I just remind them that they should avoid foods that will cause allergy and to finish their scheduled vaccinations, reassure them that it's okay", (HCW3)

However, one provider's opinion diverged and stated that patients –

"…are afraid of the side effects. Some say that they might die, die faster, or they may get rabies after getting the vaccine." (HCW1)

5. Patients' Knowledge of Rabies Disease

All providers believed patients accessed the ABTC with a baseline knowledge of rabies diseases and the severity of infection. This is illustrated by one provider's statement –

"…most of them are aware of the sequela of the rabies, since it is 100% mortality" (HCW6)

This disease knowledge and accurate perceived severity leads to vaccine seeking behaviour which providers detailed in quotes in the following section.

6. Vaccine-Seeking Behaviour

Providers believed that patients' disease knowledge also encompassed the need for immunisation which led to vaccine seeking behaviour –

"So, most of Filipinos are already aware of the effect of this rabies, so they would usually go to San Lazaro hospital to have their shots" (HCW6)

The DOH has been conducting health promotion and rabies awareness activities including the distribution of educational flyers, health information campaigns on

news media, and rabies education in school programs [73]. One provider attributed vaccine seeking behaviour to increased education –

> *"I think now because people are educated, and they know that rabies really can cause death… they sometimes call in our trunk line [hospital phone] to ask if they're scheduled and how the process is so they can get the vaccine because they already know the possibilities [consequences] if they can't get the vaccine."* (HCW5)

Providers believed vaccine seeking behaviour is driven by the perceived benefits of vaccination further evidenced by the lack of vaccine hesitancy which is described in the following section.

7. Vaccine Hesitancy and Counselling Patients

Of the five doctors and nurses interviewed, two stated they had not encountered vaccine-hesitant patients while three reported less than 1% of patients seen were hesitant about the vaccine.

> *"…it's one to nil [declining]. Most of the patients here are eager to have their vaccination shots. Because they really want anti rabies vaccine because most of them are afraid of rabies infection."* (HCW6)

Of the three that reported encountering hesitance, one provider stated the only reason they had heard from patients was travel distance –

> *"…because they're coming from a very far distance, like three hours distance by car. So, they will refuse getting the vaccination here in San Lazaro. They prefer animal bite centres or hospital nearby them."* (HCW2)

Another provider stated that patients –

> *"…sometimes ask, do I have to complete this? … they say they don't want it; they don't need it since they don't feel any pain, the dog is okay."* (HCW1)

This quote illustrates that providers encountered patients who were making vaccine decisions based on a perceived susceptibility due to the perceived health of the dog.

Two providers discussed that if patients showed hesitancy they counselled them, demonstrated by this quote from one provider who stated that –

> *"…after providing them health education or teaching, telling them the importance of the vaccine, they allow us to give them the vaccine, they change their mind."* (HCW8)

Overall, providers held the view that hesitancy was not a cause for lack of vaccine adherence as it was rarely an issue, and when encountered, quickly resolved with counselling.

Based on providers' perceptions, there was high vaccine seeking behaviours and minimal hesitancy. However, adherence can be modified by external factors. These can be positive cues to action or obstacles which prevent vaccine uptake. Provider perceptions of these potential facilitators and barriers are described in the following sections.

8. Potential Barriers

When asked the reasons they believed patients were delayed or did not adhere to vaccine schedules, providers cited transportation costs, work schedules, fear of side effects, the procedures and lines at the ABTC, and specific to COVID-19 – the lack of transportation during lockdowns.

> *"Yes, sometimes they're explanation is they have work, they don't have time to go because the schedule is not match on their work schedule."* (HCW4)

> *"Yes, there are patients like that [that don't want to collect vaccine] because they don't want to line up. They don't want to comply with the requirements."* (HCW4)

> *"During this last pandemic, their transportation or the place was in lockdown, or number one is money."* (HCW7)

Two providers stated patients are usually on schedule but when not, the most frequent cause of delayed doses, often by two to three days, was due to patients who had travelled to their hometowns where they were unable to access ABTCs –

"Sometimes they forget because they went to the province." (HCW1)

"…But on an average month where there are no holidays in between their schedules, almost all of the time they come on schedule, unless due to certain uncontrolled events like illness." (HCW8)

In contrast to these two providers, one provider believed delays were due to patients deprioritising their vaccination or sometimes misunderstanding the schedule –

"Some maybe because of miscommunication and others are those who have busy parents, so, they are tired of coming back. So that is usually the problem, tiredness, laziness, irresponsibility, and then at times, miscommunication. They thought they were advised to follow up on these days, however, they missed to see the schedule given to them. So that would be their mistake." (HCW6)

9. Potential Facilitators

One provider stated that they observed patients deciding to receive vaccination due to encouragement from their networks –

"*I think he went to the province then forgot about it, then a friend of his told him that he should get vaccinated because the dog was a stray."* (HCW1)

While another provider believes vaccine uptake is based on patient's knowledge and fear –

"…it depends on the person, their knowledge. If they're afraid, they may get rabies right then, then they definitely will rush to the hospital." (HCW9)

Discussion

Key Findings

ABTCs across the country operate in a decentralised manner under the umbrella of the local government. As such, there may be some variability in the way different ABTCs, including SLH, operate. For example, Manila City Health Department (MCHD) oversees six districts. As of July 2022, there were four operational ABTCs and plans to open ABTCs in all forty-four health centres across the districts. As SLH is a tertiary hospital, it operates independently, directly under the Department of Health, as opposed to under the MCHD. Due to this, other ABTCs have different procedures. Discussions with MCHD informed us that the three-dose

guideline was in use, regardless of WHO prequalification status. This is important as ABTC patients likely receive messaging that three doses is adequate while they are considered incomplete at SLH. This requires further investigation from patients' perspectives.

While providers state that all patients receive vaccines regardless of financial capability due to the "Malasakit Centre", the different costs, procedures and duration of visits when "donated" vaccine versus "purchased" vaccine may affect patient experience, attitudes, and adherence. The total cost at the ABTC over 4 visits when vaccines were free was ₱143 (£2.50), while paid was ₱1,179 (£20) or ₱4,287 (£70) for ID or IM respectively. Although financial assistance is available, many patients were heard complaining about the costs and the necessity to pay for vaccines themselves. Furthermore, the need to for vial sharing is an observable bottleneck in the system. In addition to this, the increased time spent at the ABTC due to the need to go through "Malasakit Centre" processes, indicates patient experience differs significantly based on the type of vaccine available. Doctors commented in informal conversation about a marked decrease in new patients during the July 2022 period when vaccines were not free, which they associated to word of mouth at the hospital gates about the cost of vaccines. Studies have shown that patient experiences at clinics, including wait times and appointment scheduling, have an impact on human papillomavirus and influenza vaccine uptake [194-196]. While there is no evidence for rabies vaccine uptake, these ABTC processes could affect patient experience and consequently, the level of adherence during periods when vaccines are not free. Additionally, this has ramifications for any retrospective analysis of vaccine uptake as it would be imperative to know when the vaccine was provided freely or not, to consider potential impacts of vaccine cost on vaccine completion.

Based on the availability of financial assistance through the “Malasakit Centre”, in theory, cost should not be a hindrance to vaccination. It is therefore the indirect costs such as transport and wages lost while taking time off work which are the important financial factors to consider. This is supported by published literature; the most reported reason for poor vaccine adherence was a lack of time and work constraints, identified in eight studies [74, 144, 150, 154, 163, 167, 186, 197]. Five studies reported distance as a barrier to vaccine uptake which could be a proxy for cost of transportation [148] (106 [155] [151] [74].

As the COVID-19 pandemic continues to affect the globe and healthcare services [198, 199], it is essential to evaluate how the pandemic may have affected patient experiences. No observations were carried out during the height of the pandemic or lockdowns in Metro Manila therefore, it is difficult to assess changes and their impact. The only observed differences post-lockdowns were face-shield and mask requirements, and a change in the waiting area for vaccination from indoors to outdoors. Although these observations are not systematic and cannot properly evaluate the effects of the pandemic, it appears that the current guidelines are not affecting service delivery. However, during an ongoing pandemic patient behaviour can change, and the fears related to contracting diseases in healthcare settings can affect vaccine uptake [200-202].

Overall, providers believed that vaccine costs and hesitancy had minimal effects on vaccine uptake. Many providers believed that the common knowledge and therefore, patients’ preexisting understanding, of the severity of rabies and the need for vaccination were the main drivers of vaccine uptake. The barriers most frequently discussed were transportation costs, work commitments and fear of wage loss, and travel to the province which resulted in delays. The former two, transportation costs and work commitments, supports evidence

identified in the 2018 study conducted in the Philippines which reported “no time” and “no money” as main influencers of poor adherence [74]. Further reasons cited by providers in this study such as the long lines and procedures at the ABTC being hindrances to patient return, are also reflected in the prior study in the Philippines which reported “ABTC being too busy” as a reason patients did not adhere to their vaccine schedule [74].

While providers’ perception of patients’ vaccine confidence is high, one provider’s opinion diverged from the group stating he believed some patients think they can get rabies from the vaccine. This misperception could lead to poor vaccine uptake, and it is important to explore vaccine hesitancy in patient populations.

Strengths and Limitations

As a context-setting, formative study, this study capitalises on multiple research methods which is a key strength. Each method captures different aspects of the ABTC processes and therefore builds a full picture of the ABTC operations. Document reviews provide insight into vaccination guidelines, patient data collected, and information distributed during ABTC visits. Patient-provider observations showed patient flow and experiences through the ABTC. Lastly, provider interviews gave further insight into ABTC processes and highlighted potential facilitators and barriers to vaccine uptake.

Observations were conducted at multiple timepoints, prior to and after the onset of the COVID-19 pandemic, which is a further strength of this study as it provided insight into changes that can occur during a disease outbreak. Furthermore, multiple observations provided an opportunity to understand the ABTC processes when “donated” vaccine was in use and when unavailable.

It is important to note the role and influence interviewers have in data collection. A limitation of this study is, as a non-national of the Philippines, the interviewer OKO was regarded as a foreigner who may have limited knowledge of the systems and the people the providers serve. This is illustrated by this quote describing people's fear of COVID-19 in medical settings potentially impacting vaccine-seeking behaviour – *"Yes. It depends on the class. If it's class ABC. Yes, they are really afraid. For those who are in class C, D, or low-income class. I think they're more of a resilient spirit. They can go out, they laugh but they're really not aware of the effect of the COVID infection. So, I think that's the resilience of being a Filipino".* The provider aims to educate the interviewer about culture and people in the Philippines. The interviewer is perceived as an outsider which may impact the comfort level of providers during their interviews, and there might have been a need to show a polished version of the ABTC setting.

A limitation is the possibility of social desirability bias affecting participants' responses in terms of how services are offered, including the level of counselling and information offered to patients [203]. Study design intended to mitigate this limitation. Social desirability bias has been theorised to be mitigated with the use of a mix of direct and indirect questioning [204], the latter of which poses questions more generally, e.g. what information is given to patients at the ABTC versus what information do you give to patients. While indirect questioning is difficult in an interview based on provider practices, a strong rapport was built with interview participants before and during the interview, another method theorised to reduce social desirability bias [205-207]. Additionally, as providers volunteered their time and only those who were willing to speak with the interviewer enrolled in the study, it is likely that there honest responses were provided. Furthermore, providers' perspectives

were sought on patient experiences, which puts the interviewee in the position of an expert where they are willing to talk freely and not burdened by the idea they are being judged.

This qualitative study is not meant to be generalised across settings but provides context for this vaccination environment. Additionally, this study sought to understand providers' perspectives on patient experiences, and potential barriers and facilitators, therefore it does not take into account information from the patients and guardians who are directly impacted. A prospective mixed-methods study was conducted following this study which explored patient perspectives and factors associated with vaccine uptake (*manuscript under preparation)*.

Conclusion

In conclusion, the SLH ABTC is a complex system which provides low-cost rabies PEP vaccination. Depending on when patients visit the ABTC, they can receive low-cost, low-hassle vaccination but at other times they may face more hurdles. There are potential barriers to vaccine uptake including transportation costs, work schedules, lack of access to ABTCs in the province, fear of side effects, time-consuming queues and procedures at the ABTC, and specific to COVID-19 – the lack of transportation during lockdowns. Potential facilitators may be found in individuals' social networks. Data derived from this study indicates that programmatic efforts to increase access to ABTCs outside the NCR, in addition to streamlined processes and increased education at ABTCs, may improve vaccine uptake. Further research on the barriers and facilitators of vaccine uptake from patients' perspectives is key to reinforce the need for these solutions or investigate other points of intervention. Therefore, a prospective cohort study enrolling patients at their first ABTC visit was conducted (*manuscript under preparation)*.

5 Study 2: Retrospective Analysis of Rabies Vaccine Completion

Rabies Vaccine Completion at a Large Animal Bite Treatment Centre: A Retrospective Database Analysis

Summary

Study 2 partially fulfilled objective 2 of characterising adherence to the rabies vaccine schedule. A retrospective analysis of 310,692 patients at SLH ABTC from 2016-2021 was conducted. 27% of patients completed a vaccine schedule of 4 doses, however 54% received 3 or more doses which may be adequately protective. Patients were 50% female, 27% under age 16, and 84% resided in the NCR. Logistic regressions conducted reported no statistically significant associations between vaccine completion and demographic characteristics or rabies exposure type. There was a decline in patients accessing the ABTC during the COVID-19 pandemic while there was a recorded rise in rabies deaths at SLH, from 43 in 2019 to 65 in 2021.

Introduction

This chapter presents a retrospective analysis of the San Lazaro Hospital database to describe the populations that access the ABTC, quantify completion of vaccine schedules and assess factors associated with adherence. Background literature on rabies epidemiology, prevention strategies, immunisation programs, and vaccination schedules are covered in the thesis background, Chapter 1. Relevant vaccine details and schedules in use at SLH are summarised below.

The Philippines' DOH vaccine recommendations are summarised in Table 5.1. This includes modifications based on immune status and the use of non-WHO prequalified vaccines.

	Categories of Contact with Suspected Rabid Animal		
	Category I	Category II	Category III
Immunologically naïve	Wash exposure site. No PEP required[2]	Wash wound 2-site ID on days 0, 3, 7, 28[3,4]	Wash wound 2-site ID on days 0, 3, 7, 28 RIG[5]
Previously vaccinated[1]	Wash exposure site. No PEP required	Wash wound 1-site ID on days 0, 3 **OR** 4 site ID on day 0	Wash wound 1-site ID on days 0, 3 **OR** 4 site ID on day 0
1 - PrEP or PEP days 0 & 7. Vaccination not recommended if PEP completed <3 months 2 - Antibiotics & tetanus vaccine may be administered 3 - 3 doses only for WHO pre-qualified vaccines 4 - 4th dose is not administered if the biting animal is alive on day 14 5 - Human RIG is used if reactive to equine RIG Immunocompromised patients with category II or III exposures receive RIG and 1-site IM on days 0, 3, 7, 28			

Table 5.1 Rabies PEP Recommendations in the Philippines. Adapted from National Rabies Control Program [73, 79, 83]

Following a DOH mandate in 2016, rabies vaccine is to be offered free in ABTCs across the Philippines while equine- and human- RIG vials are subsidized at a cost of approximately 2,400 to 14,000 PHP (£36-215) respectively [82, 114, 115].

Although rabies PEP costs are low at ABTCs, the limited data available on rabies PEP initiation and adherence in the Philippines reports low vaccine uptake. A study conducted in 2008 reported that only 54% of patients returned for their second dose, 44% for their third and 32% for their fourth [120]. These coverage data are likely to be an underestimate as patients may have received follow-up doses from a different health centre which would not be recorded in the system. Furthermore, as the policies for free PEP were introduced in 2016, these data are outdated. A 2018 study across three provinces in the Philippines showed 78% of 1,105 patients completed their vaccine series. However, this ranged across areas, with some barangays (village equivalents) having completion rates of 60% [74].

This study aims to expand the knowledge base of the proportion of rabies vaccine completion, and the factors associated with adherence using ABTC data from a different region and a dataset larger than any studies carried out in the Philippines after the provision of free rabies PEP in 2016. The study design tested the null hypothesis that factors such as

demographics and rabies exposure cannot predict vaccine adherence outcomes, and the alternative hypothesis that these factors can predict vaccine adherence outcomes with statistical significance.

This study was carried out at San Lazaro Hospital (SLH). It receives the most animal bite patients across the Philippines, approximately 100,000 a year and up to 500 a day.

Methods

The retrospective data analysis was conducted at SLH which is a tertiary referral health facility for infectious diseases located in Manila, National Capital Region (NCR). Rabies patients are transferred to SLH from across the NCR, Central Luzon and Calabarzon. The latter two regions report the highest rabies deaths in the Philippines [73], therefore it is likely that potentially rabies exposed patients are seeking PEP at the SLH ABTC. The ABTC, situated in the hospital's outpatient department, receives all potentially rabies exposed cases i.e. all animal bite cases except snake bites which are taken to the emergency department.

Deidentified individual level data from 2016-2021 were extracted from the integrated hospital management information system (iHOMIS) by the San Lazaro Hospital Epidemiology Department. Records of all patients who received a first dose rabies vaccine at the ABTC were extracted. Data variables requested included age, gender, address, exposure category, animal type, vaccine administration (dates and dose number) and RIG administration (date and dosage). Data variables received are detailed in the annex. A data quality check to ensure hospital IDs were not repeated across multiple patients was requested. The SLH Epidemiology department conducted this by performing a manual check on a random sample of 100 patient IDs and full names. Rabies case count data by year were also

extracted. Rabies deaths in the database are deaths recorded at SLH after a patient received a clinical diagnosis of rabies.

Data were extracted into Microsoft Excel [208], and imported into STATA [209] for data analyses. Data were collapsed and explorative data analysis was conducted. The proportion of vaccine completion, defined as receiving four or more vaccine doses, was established. Descriptive analysis using percentages and chi-square tests was used to show the demographic characteristics of the population accessing the ABTC and to determine if there was a statistically significant difference in groups accessing the ABTC. To assess factors associated with vaccine completion, univariable logistic regression analyses were carried out with the independent variable of vaccine completion and the dependent variables of age, gender, region of residence, and bite type. RIG administration was excluded as a variable for analysis as it was not recorded systematically as a structured categorical data field. It was recorded sparingly for some patients in a note field, a data column for free-form comments which healthcare providers could record descriptions or additional data. Results were considered statistically significant if p-value <0.05.

Results

1,037,664 records were extracted from the SLH iHOMIS database. No records were available from October to December 2017. There were 865,322 records after duplicates were dropped, and therefore the total patient throughput was estimated average of 144,200 per year. Figure 5.1 displays the yearly patient throughput which includes all patient visits from first to last dose visit. The database was then collapsed by hospital identification number, resulting in 310,692 individual patients who visited the SLH ABTC between 2016 to 2021.

Demographic characteristics of the patients are shown in Table 5.2. Patients were 50.4% female, with the largest age group being patients under 16 years of age (27.2%). 83.7% of patients lived in the National Capital Region (NCR) where SLH is located, and 71% of patients' exposure was due to a dog.

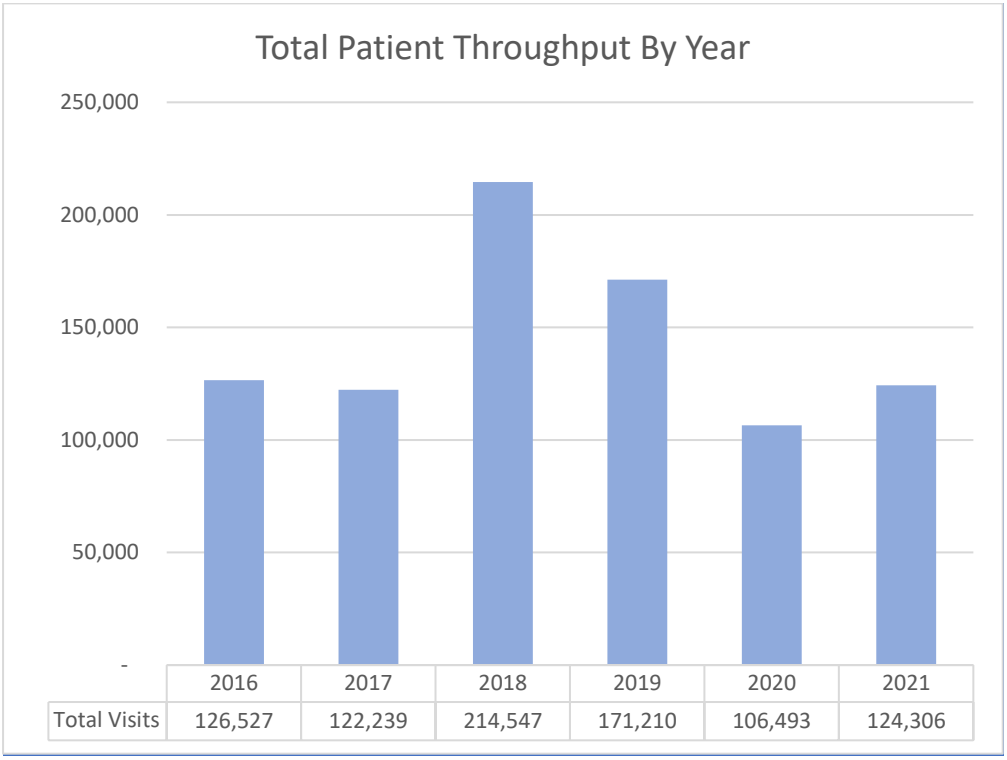


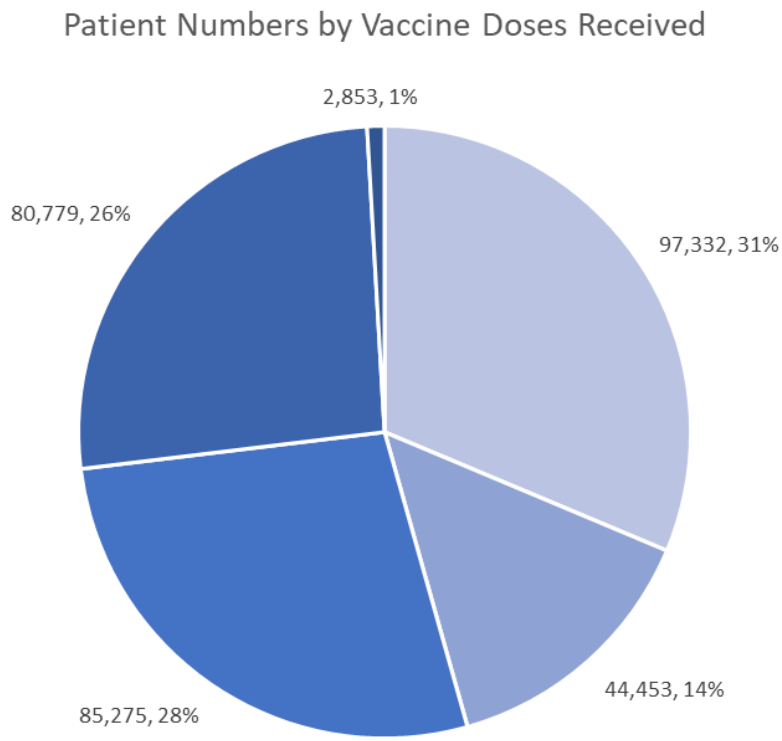
Figure 5.1 Total patient throughput at SLH ABTC from 2016-2021. Includes all vaccine visits.

Characteristics	N (%)
Total	**310,692**
Sex	
Female	156,491 (50.4)
Male	154,201 (49.6)
Age	
<16	84,397 (27.2)
16-30	58,169 (18.7)
31-45	36,797 (11.8)
46-59	28,313 (9.1)
60+[1]	17,359 (5.6)
Unknown	85,657 (27.6)
Region	
NCR	260,093 (83.7)
IV Calabarzon	15,803 (5.1)
III Central Luzon	8,084 (2.6)
Other	1,592 (0.5)
Unknown	25,120 (8.1)
Animal Type	
Dog	220,759 (71.0)
Cat	89,933 (29.0)
Exposure Category	
Category I	9 (0.2)
Category II	4,572 (83.7)
Category III	882 (16.1)

Table 5.2 Demographic and exposure characteristics of patients seeking PEP at SLH [2016-2021]

Of the 310,692 patients who sought their first-dose rabies PEP at SLH between 2016 to 2021, there was evidence that 26.9% received a complete vaccine schedule of 4 or 5 doses. Figure 5.2 shows patient numbers by the number of doses they received.

[1] Senior citizens receive priority service in fast lanes at health facilities.



Doses	Patient Numbers
1	97,332
2	44,453
3	85,275
4	80,779
5	2,853

Figure 5.2 SLH ABTC patient numbers by number of vaccine doses received

Figure 5.3 illustrates the number of patients visiting the SLH ABTC and the completion proportion per year. Overlayed on this graph are rabies cases per year, the highest case count was 68 in 2018, the same year with the lowest vaccine completion of 12.2%.

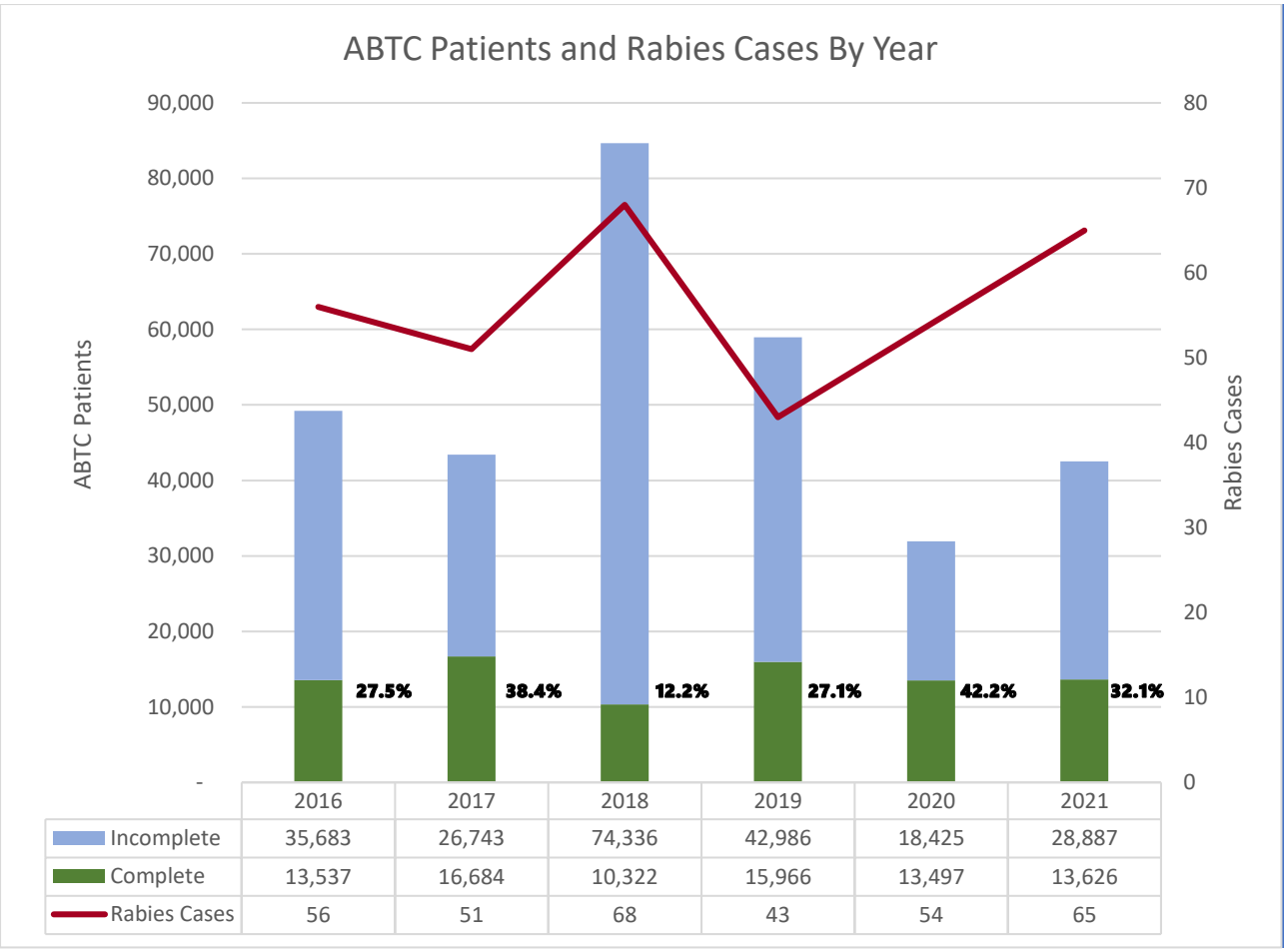


Figure 5.3 Patients accessing SLH ABTC for PEP showing proportion of complete (4+ doses) and incomplete vaccination by year. Rabies cases at SLH are overlayed.

The results of logistic regressions carried out with the available demographic and exposure data are displayed in Table 5.3. Odd ratios showed no statistically significant associations between patient demographics, rabies exposure and vaccine completion therefore proving the null hypothesis that factors such as demographics and rabies exposure cannot predict vaccine adherence outcomes.

Characteristics	Complete N (%)	Incomplete N (%)	Odds Ratio [95% CI]
Total	83,632 (26.9)	227,060 (73.1)	
Age			
<16	27,717 (32.8)	56,680 (67.2)	REF[1]
16-30	16,121 (27.7)	42,048 (72.3)	0.78[0.76-0.80]
31-45	11,934 (32.4)	24,863 (67.6)	0.98[0.95-1.00]
46-59	10,692 (37.8)	17,621(62.2)	1.24[1.21-1.28]
60+	6,605 (38.0)	10,754 (62.0)	1.26[1.21-1.30]
Sex			
Female	43,666 (27.9)	112,825 (72.1)	REF
Male	39,966 (25.9)	114,235 (74.1)	0.90[0.89-0.92]
Region			
NCR	69,903 (26.9)	190,190 (73.1)	REF
IV Calabarzon	3,451 (21.8)	12,352 (78.2)	0.76[0.73-0.79]
III Central Luzon	1,898 (23.5)	6,186 (76.5)	0.83[0.79-0.88]
Other	223 (14.0)	1,369 (86.0)	0.44[0.38-0.51]
Animal Type			
Dog	58,528 (26.5)	162,231 (73.5)	REF
Cat	25,104 (27.9)	64,829 (72.1)	1.07[1.05-1.09]

Table 5.3 Completion status and odd ratios of adherence by patient demographics

Discussion

Key Findings

This retrospective data analysis shows low rabies PEP vaccine completion at SLH and an unfortunate upward trend in rabies deaths between 2019 and 2021. The 27% completion falls far below the DOH's target of 90% completion and will undermine the countries goals to eliminate human rabies by 2030 [73]. However, 54% of patients received at least three doses, the same proportion as in a 2016 study conducted in Muntinlupa, NCR [100]. While SLH recommends 4 or 5 doses as a complete vaccine schedule due to the use of non-WHO prequalified vaccines, the WHO published guidelines recommending the use of a 3-dose schedule [95], therefore the 54% of patients who received 3 or more doses may be adequately protected. This suggests that with the use of WHO prequalified vaccines the

[1] REF is the reference category of comparison in the logistic regression models. The odds ratios (OR) presented are in comparison to the reference category.

completion rates will be higher, representing progress and an opportunity to target those who do not return for their third dose as opposed to the larger task of fourth dose retention. The 27% vaccine completion is very low in comparison to a prospective study which was conducted in 2018 in Bohol, a province of the Philippines, which reported a 78% dose completion [74]. This large difference in vaccine adherence may highlight the limitations of a database analysis as it does not take into account participants receiving follow-up doses at other sites or the possibility of missing data.

27% of the patients seeking rabies PEP in the ABTC were aged under sixteen. The proportion of patients under age sixteen receiving PEP reflects the rabies epidemiological situation in the Philippines, as a third of all rabies deaths occur in children [77], and is close to the global average – 40% of deaths occur in children [18]. On the contrary, the PEP administration age demographics in SLH differs from the national PEP data, as 44% of all animal bite cases were reported in children below fifteen [73].

At the SLH ABTC, 50% of patients were female and 71% had exposures caused by a dog. Therefore, while age differs in the demographics of national animal bite cases, similarities between national and SLH ABTC data are reported in sex, 50% female; and animal exposure, 70% of which are dogs. The proportion of people at SLH by category of exposures differs from the national data. At SLH, 84% had category II exposures while 16% had category III exposures, while at the national level 73% had category II and 27% category III exposures [73]. These similarities between SLH ABTC and national demographic data of patients reporting animal bites are important as it shows information derived from SLH, including completion data, could be extrapolated across the Philippines.

San Lazaro Hospital attends to a high number of potential rabies-exposed patients. 865,322 vaccine doses were administered between 2016 and 2021. With an average of 144,200 patients per year, and open six days a week, therefore the ABTC is attending to approximately 460 patients per day. Studies have shown that the use of intradermal vaccination in high patient throughput situations reduces the per person cost of rabies vaccination [210, 211], without a reduction in immunogenicity [138, 139]. This is because intradermal administration is more vial- and volume- efficient and therefore reduces vaccine wastage [210, 211]. However, with such a high patient load, the possibility that vaccines are being overprescribed could be considered, and even reduced patient numbers would still reach the threshold for cost-effectiveness [212]. There have been discussions around the over prescription of PEP and the need for improved risk assessments to reduce vaccine costs and burdens on ABTCs. This is important as countries trend towards elimination. A study conducted in Bohol in 2019 showed that 92% of patients were bitten by a healthy dog, and improved risk assessments could halve the expenditure on PEP [213]. However as rabies is 99% fatal [13], clinicians are hesitant to limit PEP prescriptions, as one study showed that clinicians did not always make assessments for PEP prescription with a full exposure history, basing it solely on the fact that the individual was bitten by a dog [214].

The ABTC received the highest number of patients in 2018 compared to other years. There was also an increase in rabies cases. However, data to explain this increase are limited. There were no apparent changes to the exposure risk assessment, cost of vaccine, or data recording system. SLH staff recollected mass education campaigns in 2018 and proposed that the increase in rabies awareness due to the campaign events could have led to the high numbers of individuals seeking PEP. The number of rabies awareness events have been on

the rise in the Philippines, documented by the number of registered World Rabies Day campaign events which rose from 10 in 2012 to 76 to 2015 [215].

Impacts of the COVID-19 Pandemic on Vaccine Uptake

In 2020, 31,922 patients sought care at the ABTC, a decrease of 27,000 people compared to the year prior. This is likely due to the impacts of COVID-19 across three fronts. Firstly, from the start of COVID-19 pandemic in March 17 to May 15, the Luzon Island which comprises the NCR, Central Luzon and Calabarzon, the areas which SLH serves, were under enhanced community quarantine (ECQ) [216, 217]. The ECQ restricted people's movement, prohibited the operation of public transport, and directed for physical distancing protocols of one metre. The ECQ was downgraded to general community quarantine (GCQ) [218, 219], which had less restrictions but jeepneys, the most common form of public transport were not allowed back on the roads until July 13, 2020, and still required a 50% capacity limit and significant modifications [132]. Between March 2020 and September 2021, Metro Manila rotated between ECQ, GCQ and other forms of restrictions [192, 220, 221]. This severely limited movement and the ability to seek healthcare [222], and therefore the number of people accessing SLH ABTC. Secondly, triage screening at the SLH gate prevented those with cough, fever, or other COVID-19 symptoms from accessing the ABTC. The third factor is based on anecdotal information that due to the lockdowns and restriction of movement, there were less dog-human interactions and therefore less opportunities for rabies exposure. While these factors led to lower number of patients at the ABTC, there was also an interruption to mass canine vaccination campaigns [223], and these factors may be the causes of the increase in rabies risk, as deaths increased year-on-year between 2019 and 2021. These issues of interruption to canine vaccination and reduced access to PEP during

the pandemic were identified in other Asian countries [224]. Preliminary data have reported increased rabies deaths during the period of the pandemic in endemic countries such as in Peru [225] and Iran [226].

Strengths and Limitations

This study utilises six years of data at the ABTC which receives the most patients in the Philippines, producing a study population of over three hundred thousand. This robust dataset is the key strength of the study. It provides new data to fill a knowledge gap on rabies vaccine completion in the National Capital Region, and it is the largest analysis of vaccine completion in the Philippines after the introduction of free rabies PEP in 2016. However, there is a limitation in the dataset due to the missing data from October to December of 2017.

A limitation of this study is the fact that the retrospective study design does not take into consideration vaccine doses received by patients at other ABTCs, therefore the proportion of adherence may be higher. Some studies have shown that patients will receive their follow-up vaccines at ABTCs closer to their home than the initial ABTC they visited [159]. A further limitation is the fact that medical history is not collected in these databases. Consequently, vaccine completion is based on the dose recommendation for immunocompetent patients which may not reflect true completion for immunocompromised patients who require an additional dose. Lastly, delays in initiation are not described as the rabies exposure date is not available.

Conclusion

This study gives a baseline understanding of the population accessing rabies post-exposure prophylaxis at the largest ABTC in the Philippines and quantifies vaccine completion. While

it is not possible to conclusively state these data are representative of the Philippines due to San Lazaro Hospital's urban location, size, and community recognition, it adds new knowledge on this population to the current literature.

Further research on vaccine completion rates through a prospective study is essential to investigate whether all vaccines doses are documented at SLH, whether that be due to follow-up doses being received at other clinics or missing data records. This would provide a more accurate assessment of vaccine completion and an opportunity to assess the factors related with vaccine completion, in order to implement solutions to improve retention.

Due to the large amounts of vaccines prescribed at SLH, an evaluation of risk exposure assessment guidance, and the provision of supplemental training may reduce vaccine use without compromising safety. The cost savings could be directed to programming to increase vaccine uptake.

The permanent use of WHO prequalified vaccine is highly recommended as it would result in higher vaccine completion and disease protection based on the higher proportion of patients who received at least three doses compared to four doses, 54% and 27%, respectively. This is the recommendation of the WHO [91] [95], however due to costs and supply chain issues, San Lazaro Hospital has not instituted this policy. This is the case in many LMICs as a study reported that only 27% of the 23 African and Asian countries surveyed in 2017-2018 used WHO prequalified vaccines exclusively [82]. This results from this study at SLH show how imperative it is for prequalified vaccine to be used.

6 Study 3: Prospective Mixed Method Study on Rabies Vaccine Uptake

Overview of the Prospective Mixed Method Study Design

This mixed method study was conducted using an explanatory sequential design [227], wherein the quantitative data collection and analysis were conducted prior to the qualitative strand. Participants were enrolled and surveyed during their first-dose vaccine visit. Following this, a subgroup of participants was invited to participate in in-depth interviews at the end of their vaccine schedule. This study design was adopted to use descriptive qualitative data to further contextualise survey data and deepen understanding of the factors related to vaccine adherence. This approach has been used in vaccine hesitancy and uptake studies [228-232].

This chapter presents the study in two research paper manuscripts which will be submitted and published in sequence; therefore, the second paper will appropriately cite the first.

6.1 Quantitative Study

Research Paper Cover Sheet

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed <u>for each</u> research paper included within a thesis.

<u>SECTION A – Student Details</u>

Student ID Number	1807686	**Title**	Ms
First Name(s)	Oladeji		
Surname/Family Name	Oloko		
Thesis Title	Factors Associated with Vaccine Uptake: A Study on Rabies Post-Exposure Prophylaxis in The Philippines		
Primary Supervisor	Chris Smith		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

<u>SECTION B – Paper already published</u>

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

<u>SECTION C – Prepared for publication, but not yet published</u>

Where is the work intended to be published?	PLOS Neglected Tropical Diseases
Please list the paper's authors in the intended authorship order:	Oladeji K Oloko, Ferdinand De Guzman, Ana R Sayo, Mary-Ann Salazar, Shuichi Suzuki, Pauline Paterson, Chris Smith

Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived and designed the study, carried out data analyses and drafted the manuscript. CS and PP provided feedback and guidance for study conceptualisation and analysis. MS conducted participant recruitment. All authors provided comments on the manuscript.

SECTION E

Student Signature	
Date	22/05/2023

Supervisor Signature	
Date	19/09/2023

Rabies Vaccine Uptake in the Philippines: Quantifying Schedule Completion, Vaccine Confidence, and Factors Associated with Adherence

Abstract

Rabies, a fatal vaccine-preventable disease, is endemic in the Philippines where there are an estimated 377 annual deaths. Vaccination can be administered pre- or post- exposure, the latter most often used in endemic settings. The Philippines Department of Health (DOH) aims to offer free vaccination through animal bite treatment centres (ABTCs) across the country. The DOH recommends a three-dose vaccine schedule when WHO prequalified vaccine is available while a four-dose schedule is used when WHO prequalified vaccine is not available. This study aimed to quantify vaccine completion, explore immunisation attitudes, investigate factors associated with uptake, and identify barriers to adherence through a prospective cohort study at an ABTC in Manila.

The study enrolled 506 participants during their first-dose vaccine visit. Participants then received a call following the end of their vaccine schedule to assess vaccine completion through self-report. Descriptive statistical analysis was used to establish the demographic characteristics of patients accessing the ABTC. Logistic regression analyses were carried out to assess factors associated with vaccine completion. Vaccine completion was defined as four doses, or three if the animal of exposure was alive on day fourteen.

Study participants were mostly 62% female, 50% secondary school educated, 75% owned pets and 58% lived in Manila City. 63% of participants visited the ABTC within one day of exposure. 86% of study participants completed their vaccine schedules. Females and participants aged 60+ had higher odds of vaccine adherence.

Rabies vaccine confidence was high. 84% of participants strongly agreed that rabies vaccines were safe and effective. Participants had lower confidence in COVID-19 and dengue vaccines, only 66% and 51% strongly agreed.

The main barriers to vaccine uptake reported were a lack of time, the inability to access ABTCs when travelling outside Manila, and forgotten schedules. While vaccines are provided free or at subsidised rates, indirect costs such as travel, and loss of productive time and wages, remain as barriers to vaccine uptake. Results from this study suggests that it is essential to evaluate access to ABTC across the country, and institute the permanent use of WHO prequalified vaccines in a three-dose schedule to increase vaccine completion.

Introduction

Rabies is a fatal zoonotic viral disease. Transmission occurs through exposure to a rabies infected animal, ninety-nine percent of which are due to dog bites although all mammals can transmit rabies. Globally, there are an estimated 59,000 annual rabies deaths and an estimated 377 deaths occurred in the Philippines in 2019 [70]. However, this is likely an underestimation due to underreporting and misdiagnosis [59]. Rabies is often misdiagnosed as other encephalitis causing conditions such as cerebral malaria [33], conditions with neurological symptoms such as brain tumours and strokes [20, 23], and even anecdotally, psychosis. Canine rabies is endemic in the Philippines and with approximately 1 million animal bites annually and rising, there may be a higher risk of rabies incidence than portrayed by the annual death rate [73].

Although fatal upon the onset of disease, rabies is highly preventable with timely administration of a full schedule of post-exposure prophylaxis vaccines. The Philippines Department of Health (DOH) recommends the Institut Pasteur Cambodia (IPC) intradermal

schedule (6 doses via 2 sites on 3 days. Days 0, 3 & 7) with the use of WHO prequalified vaccines [95]. However, there are periodic shortages of WHO prequalified vaccines and when a non-prequalified vaccine is used, the updated Thai Red Cross schedule 2-2-2-2-0 is used. This schedule requires two additional intradermal doses on day 28, for a total of 8 doses via 2 sites on 4 days. Immunocompromised patients receive the intramuscular Essen schedule with an additional dose – 5 doses on days 0, 3, 7, 14 & 28. This is due to concerns that non-prequalified vaccines are insufficiently immunogenic and may not confer complete protection with reduced doses. In addition to active rabies vaccination, passive vaccination in the form of rabies immunoglobulin (RIG) is given to severe exposures. The post-exposure prophylaxis (PEP) recommendation is shortened to the first 3 doses if the biting animal is still alive after 14 days as rabies infected canines and felines do not survive past 2 weeks [73]. The recommendations are summarised in Table 6.1.

	Categories of Contact with Suspected Rabid Animal		
	Category I	Category II	Category III
Immunologically naïve	Wash exposure site. No PEP required[2]	Wash wound 2-site ID on days 0, 3, 7, 28[3,4]	Wash wound 2-site ID on days 0, 3, 7, 28 RIG[5]
Previously vaccinated[1]	Wash exposure site. No PEP required	Wash wound 1-site ID on days 0, 3 **OR** 4 site ID on day 0	Wash wound 1-site ID on days 0, 3 **OR** 4 site ID on day 0
1 - PrEP or PEP days 0 & 7. Vaccination not recommended if PEP completed <3 months 2 - Antibiotics & tetanus vaccine may be administered 3 - 3 doses only for WHO pre-qualified vaccines 4 - 4th dose is not administered if the biting animal is alive on day 14 5 - Human RIG is used if reactive to equine RIG Immunocompromised patients with category II or III exposures receive RIG and 1-site IM on days 0, 3, 7, 28			

Table 6.1 Rabies PEP recommendations in the Philippines. Adapted from National Rabies Control Program [73, 79, 83]

Following a DOH mandate in 2016, rabies vaccine is free in ABTCs across the Philippines while RIG is subsidized at an approximate cost of 2,400 to 14,000 PHP (£36-215) [82]. The wide range is due to equine-RIG being significantly cheaper than human-RIG. The rising bite incidence may be due to improved reporting as well as increased healthcare seeking behaviour upon the onset of free ABTC care in 2016 [73].

However, some patients initiate vaccination and do not complete the full course. A 2018 study across three provinces in the Philippines reported that 78% of 1,105 patients completed their vaccine series. This ranged across areas, some barangays (village equivalents) reported completion rates of 60%.

Completion of the rabies vaccine schedule is essential as rabies deaths can occur and have been recorded in individuals who received partial vaccination [20, 109]. At San Lazaro Hospital, the research site for this study, retrospective analyses of rabies deaths between 1987 to 2006 and 2006 to 2015 were conducted. Data reported 2% and 10%, respectively, of rabies cases received incomplete vaccines while only 0.05% and 0.5% of the cases had a full vaccine schedule [233, 234]. The sole rabies case in the former study that reported complete vaccination was administered RIG on a delayed schedule and given incorrectly, intramuscularly instead of infiltrated around the wound. These studies show the increased risk associated with incomplete vaccination in comparison to fully and correctly administered PEP. There have been some studies conducted assessing the factors associated with rabies vaccine adherence and the reasons that limit the completion of PEP schedules. Globally, cost is a factor cited most frequently as a hindrance to vaccine uptake. However, as the Philippines provides free rabies vaccine, it is feasible to investigate the non-cost related barriers to vaccine uptake. This study aimed to quantify vaccine completion, explore immunisation attitudes, investigate factors associated with uptake, and identify barriers to adherence at the largest ABTC in the Philippines. The study was designed to test the null hypothesis that factors such as demographics, vaccine confidence, rabies exposure, and knowledge, attitudes and practices cannot predict vaccine adherence outcomes, and the alternative hypothesis that these factors can predict vaccine adherence outcomes with statistical significance.

Methods

This prospective cohort study was designed to assess vaccine adherence, knowledge, attitudes and practices (KAP), and factors associated with adherence in patients who received their first vaccine dose at San Lazaro Hospital (SLH). SLH, the study site, is a tertiary referral health facility for infectious diseases located in Manila, National Capital Region (NCR). The ABTC, situated in the hospital's outpatient department, administers rabies post-exposure prophylaxis.

The study sample size was calculated to detect a difference between participants by vaccine completion status. Using the hypothesis of 60% vaccine completion based on studies in the Philippines [74] and countries with similar rabies vaccination programs [161, 235, 236], and a potential loss to follow up of 20%, a sample size of 470 correctly completed surveys was calculated. Therefore, the target study size was set at 500 participants. The inclusion and exclusion criteria were defined as follows:

Inclusion criteria:

- Able to provide consent.
- Patients at a first-dose vaccine visit
- Recommended a full course of rabies post-exposure vaccination.

Exclusion criteria:

- Immunocompromised persons and those recommended a non-standard vaccine schedule.
- Minor without a consenting adult

Participants were enrolled following the medical assessment, after the vaccine recommendation had been made. During the 2-month enrolment period from March to May 2022, the first patient awaiting vaccination, or the guardian in cases of minors, was approached and participant screening was conducted. If ineligible, the next patient was

screened until an eligible participant was identified. Study information was provided to eligible patients through printed participant information sheets. Questions from patients were addressed. Patients were then invited to participate in the study, informed consent was discussed, and consent forms were completed. After the vaccine was administered, the patient was then escorted to an adjoining room for privacy purposes where the KAP survey was completed.

Thirty days after the first dose, all participants were called for follow up to self-report vaccine completion. Using hospital identification numbers collected at the initial survey, vaccine dose data at the registry was extracted through both paper records and the electronic database.

The Day 0 survey conducted upon enrolment was developed to collect data on sociodemographic characteristics, rabies exposure, accessibility to ABTCs, rabies knowledge, immunisation attitudes and vaccination practices of rabies exposed individuals. Survey questions on immunisation attitudes, and trust in healthcare providers and information sources were adapted from the Wellcome Global Monitor [237]. These questions were structured around a theoretical framework adapted from the Health Belief Model, Betsch's "determinants of vaccine decision making" and the WHO SAGE Working Group on Vaccine Hesitancy's "3 Cs" and "vaccine hesitancy determinants matrix" models [126]. The Day 30+ survey collected information on vaccine completion, location where follow-up doses were received, and side effects. Survey tools were developed in English, translated to Tagalog by an external translation service, adjusted by the study research assistant, and back translated to English for quality checks. Survey tools were then pilot tested. Six participants were enrolled to test the survey, after which slight wording adjustments were made for

comprehension. Participants had the option of the survey being conducted in either Tagalog or English. All participant surveys were carried out in Tagalog by the study research assistant.

Following survey completion, participants with knowledge gaps i.e. those who did not have awareness of disease severity or the required vaccine schedule, were provided information on rabies disease and counselled on the need to receive vaccination. Participants received 500 PHP (£8) as compensation for time spent.

Survey data were collected and managed using REDCap electronic data capture tools hosted at LSHTM [238-240]. Identity and contact information were collected for participant follow up and stored securely in the REDCap database. Identifiable data were removed from data downloads for analyses, and non-identifiable study IDs were used ensuring patient confidentiality.

Data were extracted from REDCap into STATA [209] for data analyses. Descriptive analysis established the demographic characteristics of the population accessing the ABTC and the proportion of vaccine adherence. A kappa statistic was calculated to assess the discordance between self-report and registry data. The primary dependent outcome was completion of the rabies PEP schedule by self-report. Completion was defined according to immunisation guidelines at SLH as four vaccine doses, which may be shortened to three doses if the animal of exposure was alive fourteen days after the exposure. To assess factors associated with vaccine completion, a predictive regression model was used. Univariable logistic regression analyses were carried out with all potential predictor variables collected during the survey. Independent variables with p-value of <0.25 were selected for the multivariable logistic regression. The final model was built using stepwise elimination. Variables with a p-

value of <0.05 were considered to be statistically significantly associated with vaccine completion. Covariates that changed odds ratio coefficients by 10% or greater were considered confounders and kept in the model.

The study protocol was approved by the London School of Hygiene & Tropical Medicine (LSHTM) Research Ethics Committee (LSHTM Ethics Ref: 22718. 29/10/2021) and the San Lazaro Hospital Research Ethics Review Unit (SLH-RERU-2021-004-1) 21/01/2022).

Results

Study results are presented in this section in the following sequence: participant demographics and rabies exposure characteristics, vaccine confidence and immunisation attitudes, the number of doses received by participants, the proportion of vaccine completion, the odds ratios of independent variables associated with vaccine completion, and finally the reported reasons for incomplete vaccination schedules.

574 patients were approached in the ABTC of which 515 were eligible. 9 patients declined, and 506 participants were enrolled; 88% of total participants approached. Participant demographics and rabies exposure history are shown in Table 6.2. The majority of participants were female (62%), secondary school educated (50%), homeowners (65%), pet owners (75%), lived in Manila City (58%) and lived a median of 30 minutes from the ABTC.

Table 6.2 Participant demographics and rabies exposure history

Characteristics	N (%)
Total	**506**
Demographics	
Gender	
Female	313 (61.9)
Male	192 (37.9)
Prefer not to answer	1 (0.2)
Patient Age	
≤15	84 (16.6)
16-30	167 (33.0)
31-45	137 (27.1)
46-59	79 (15.6)
60+[1]	39 (7.7)
Respondent Age[2]	
18-30	171 (33.8)
31-45	182 (36.0)
46-59	100 (19.7)
60+	50 (9.9)
Unknown	3 (0.6)
Guardian Role (N=204)	
Parent	147 (72.1)
Grandparent	19 (9.3)
Sibling	6 (2.9)
Other Guardian	32 (15.7)
Education[3] (N=504)	
None	1 (0.2)
Primary school	49 (9.7)
Secondary school	254 (50.4)
Vocational	20 (4.0)
Bachelor degree or higher	180 (35.7)
Median distance to ABTC. Minutes (IQR)	30 (22-48)
City (N=504)	
Manila City	291 (57.7)
Other Metro Manila Cities	192 (38.1)
Outside Metro Manila	21 (4.2)
Income (PHP)	
<5,000	22 (4.3)
5,000-10,000	103 (20.4)
10,000-15,000	131 (25.9)
15,000-20,000	125 (24.7)
>20,000	124 (24.5)
Prefer not to answer	1 (0.2)
Homeowner	330 (65.3)
Rent (N=172). PHP (median, IQR)	3,000 (2,000-5,000)
Pet owner†	380 (75.1)
Dog	313 (61.9)
Cat	117 (23.1)
Other mammal	4 (0.8)
Other animal	2 (0.4)
Vaccinated Pet (N=380)	178 (46.8)
Rabies Exposure	
Exposure Category	
Category II	305 (60.8)
Category III	197 (39.2)
Exposure Type†	
Scratch	126 (75.1)
Bite	424 (84.0)
Multiple Bite	19 (3.8)
Exposure Site†	
Head & Neck	81 (16.0)
Arm	94 (18.6)
Finger	73 (14.4)
Torso	30 (5.9)
Upper leg	58 (11.5)
Lower Leg	187 (37.0)
Animal Type	
Participant Pet	286 (56.5)
Other's Pet	134 (26.5)
Stray	86 (17.0)
Animal Vaccine Status	
Vaccinated	144 (28.5)
Unvaccinated	248 (49.0)
Unknown	114 (22.5)
Animal Status	
Alive	457 (90.3)
Dead	8 (1.6)
Unknown	41 (8.1)
Treatment (N=499)	
None	28 (5.6)
Wound washing	452 (90.6)
Medical consultation	19 (3.8)
Prior Vaccine	86 (16.9)
RIG (N=490)	135 (27.6)

[1] Senior citizens receive priority service in fast lanes at health facilities.
[2] Adult patient or guardian of minor
[3] Education of adult patient or guardian of minor
† Multiple answers

The number of days from exposure to ABTC visit ranged from 0 to 17 days, however 63% of participants sought care within the first day of exposure and 90% of participants visited the ABTC within 3 days. This is shown in Figure 6.1.

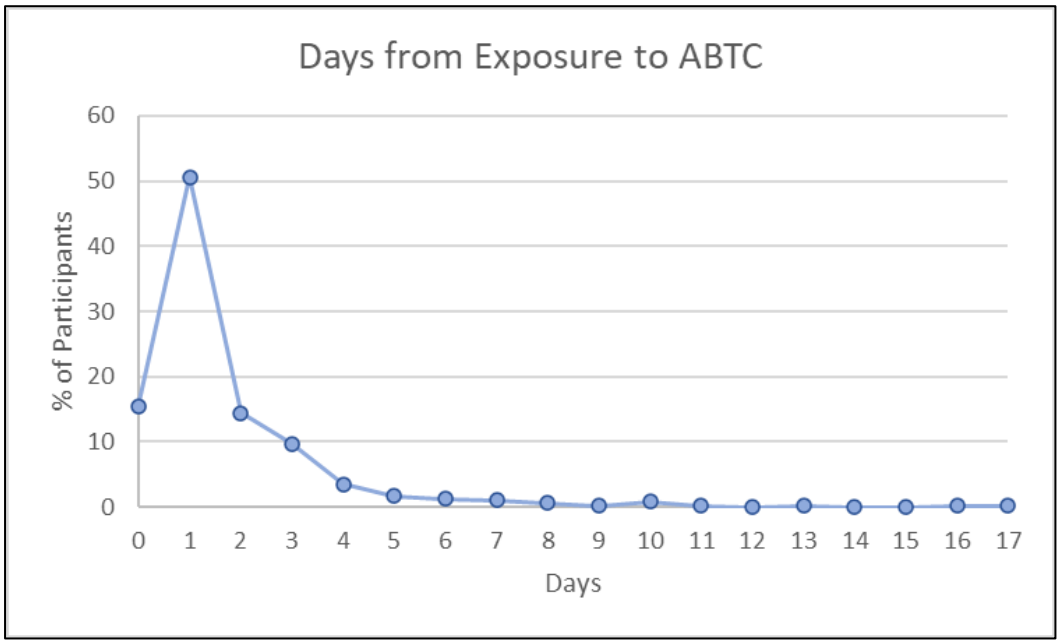


Figure 6.1 Vaccine Initiation: Days between participants' animal exposure and visit to SLH ABTC

Participants spent a median of 1hr 40 mins (IQR 60-146) at the ABTC from arrival to departure. The majority of participants reported having had a good experience with only 4% reporting issues during the visit. In the next section of the survey, knowledge of the vaccine schedule was assessed. Participants were enrolled after healthcare providers would have explained the vaccine schedule. 84% of participants reported having full awareness of the number of doses and required dates to return to complete the vaccine regimen. 6% had partial awareness, only knowing the number of doses, but not the dates to return, while 10% could not recall the number of doses or the scheduled dates.

Results of assessing immunisation attitudes and vaccine confidence are shown in Figure 6.2. Vaccine confidence, assessed at enrolment, was generally high in the study population, as all participants “agreed” or “strongly agreed” that “vaccines are important for children to

have". Confidence was high in rabies vaccine and expanded program on immunisation (EPI) vaccines' measles and tetanus, with an average of 98% agreeing that these vaccines were both safe and effective. Confidence in COVID-19 vaccines was lower. 89% "agreed", however that was made up of only 65% who "strongly agreed", in comparison to 84% in the rabies and EPI vaccines. Dengue vaccines held the lowest confidence with an average of 67% agreeing, and 51% strongly agreeing that the vaccine is safe. 20% of participants "strongly disagreed" with the safety and effectiveness of dengue vaccines, the highest proportion in all vaccines. In comparison the average of participants who "strongly disagreed" in relation to rabies and the EPI vaccines was 0%, and 3% in relation to COVID-19 vaccines.

Figure 6.2 Immunisation attitudes: participant perceptions of importance, effectiveness, and safety of vaccines

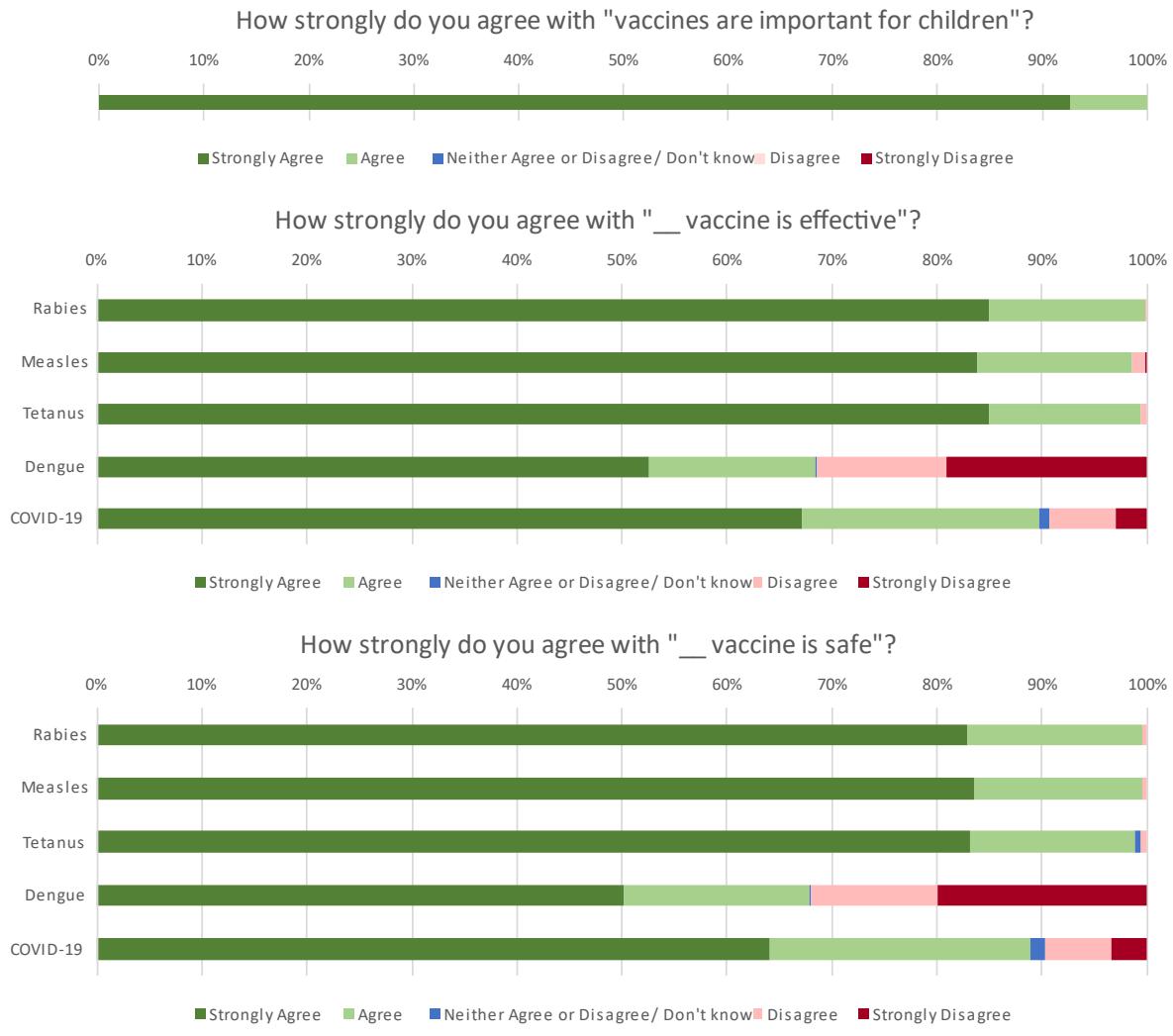
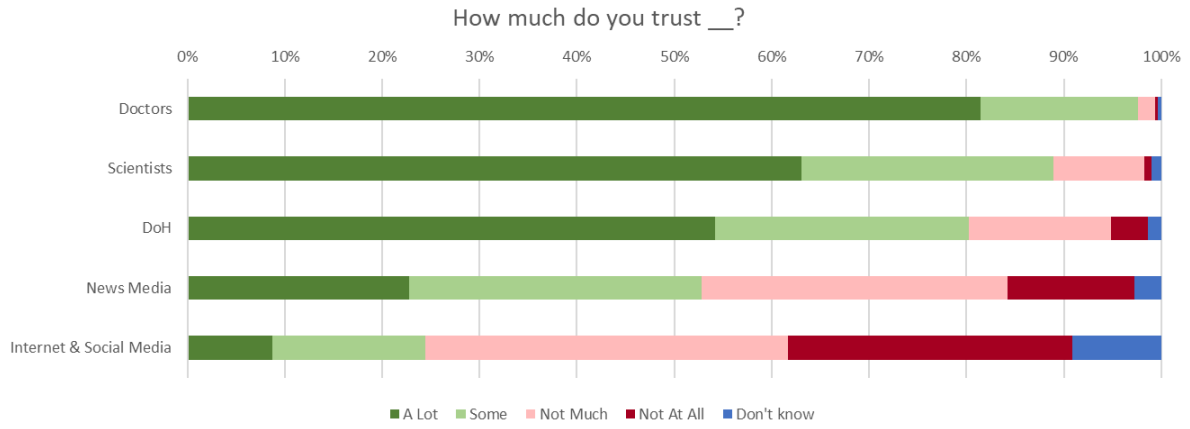


Figure 6.3 presents participants' trust in information sources with the highest trust in doctors, scientists, the Department of Health, and the lowest trust in internet & social media. Trust in news media was mixed.

Figure 6.3 Participant trust in sources of information



To assess vaccine completion, 453 (90%) of participants completed the Day 30+ follow-up survey, and vaccine dose data for 502 (99%) participants were extracted from the SLH registry records. Of the 453 participants who self-reported doses, 349 (77%) received four or more doses while according to records data, 320 (64%) participants completed the vaccine schedule.

In the self-report and records data, 413 (91%) and 387 (77%) of participants received three or more doses, respectively. These results are displayed in Table 6.3. Of the 64 participants who received three doses, 41 reported that the animal of exposure was alive. In line with the DOH guidance, patients may receive only three doses if the animal is alive after day 14 [73], therefore 390 of 453 (86%) participants received the correct dose and are considered to have completed vaccination for the analysis.

Table 6.3 Number of vaccine doses received and proportion of completion

	Self-Report	Registry
	N (%)	
Vaccine Completion		
Yes*	390 (77.1)	320 (63.3)
No	63 (12.5)	182 (35.9)
Unknown	53 (10.5)	4 (0.8)
Vaccine Doses		
1	16 (3.2)	81 (16.0)
2	24 (4.7)	34 (6.7)
3	64 (12.6)	67 (13.2)
4	343 (67.8)	319 (63.1)
5	6 (1.2)	1 (0.2)
Unknown	53 (10.5)	4 (0.8)

* 3 doses with report of animal alive is considered complete by self-report

Of the 453 participants reached for follow up, 434 (96%) stated they received all vaccine doses at SLH (16 received only the initial dose), 18 (4%) received vaccine doses at a combination of SLH and other ABTC, and 1 did not provide a response. Of these 453 participants, 110 participants had a different vaccine dose number recorded in the registry versus self-report data, representing a 24% variance in data. A kappa coefficient of -0.14 was calculated indicating discordance in the data that is likely not due to chance.

Results of the univariable logistic regressions to determine associations to vaccine completion are shown in Table 6.4. The odds ratios of independent variables are presented based on self-report and registry data for comparison. Statistically significant associations were identified for six factors. Using self-report data, participants who were female (OR 2.09, 95% CI 1.22-3.57), aged 60+ years (OR 5.03, 95% CI 1.15-21.96) or had a prior rabies vaccination (OR 2.67, 95% CI 1.03-6.90) had higher odds of adherence. While using registry completion rates, participants who had tertiary level education (OR 2.20, 95% CI 1.16-4.20) had higher odds of adherence, and those who were bitten or scratched by another person's pet (OR 0.57, 95% CI 0.38-0.87) or had visited another clinic prior to the SLH ABTC (OR 0.25, 95% CI 0.07-0.89) had lower odds of adherence.

Table 6.4 Crude odds ratios of rabies vaccine completion

	Self-Report N=453		Registry N=502	
Characteristics	**Complete N (%)**	**Odds Ratio [95% CI]**	**Complete N (%)**	**Odds Ratio [95% CI]**
Total	390 (86.1)		320 (63.8)	
Demographics				
Gender				
Male	140 (80.5)	**REF[1]**	120 (62.5)	REF
Female	249 (89.6)	**2.09[1.22-3.57]**	199 (64.4)	1.09[0.75-1.58]
Patient Age		**1.02[1.00-1.04]**		1.01[1.00-1.02]
<16	60 (85.7)	REF	53 (63.1)	REF
16-30	121 (81.2)	0.72[0.33-1.58]	98 (59.4)	0.86[0.50-1.47]
31-45	111 (87.4)	1.16[0.49-2.71]	87 (64.0)	1.04[0.59-1.83]
46-59	64 (90.1)	1.52 [0.55-4.26]	54 (69.2)	1.32[0.68-2.53]
60+	34 (94.4)	2.83[0.59-13.69]	28 (71.8)	1.49[0.65-3.40]
		1.02[1.00-1.04]		1.01[1.00-1.02]
Respondent Age		**1.03[1.01-1.05]**		**1.01[1.00-1.03]**
16-30	124 (81.1)	REF	102 (60.0)	REF
31-45	139 (86.3)	1.48[0.81-2.71]	113 (62.4)	1.10[0.72-1.70]
46-59	81 (89.0)	1.89[0.88-4.10]	66 (66.7)	1.33[0.79-2.24]
60+	43 (95.6)	**5.03[1.15-21.96]**	36 (73.5)	1.85[0.91-3.73]
		1.03[1.01-1.05]		1.01[1.00-1.02]
Guardian Role				
Parent	117 (90.1)	REF	97 (66.4)	REF
Grandparent	14 (87.5)	0.72[0.15-3.54]	14 (73.7)	1.41[0.48-4.15]
Sibling	5 (83.3)	0.51[0.06-4.76]	5 (83.3)	2.53[0.29-22.22]
Other Guardian	23 (85.2)	0.59[0.17-1.99]	17 (53.1)	0.57[0.26-1.24]
Education				
Primary school	31 (81.6)	REF	25 (51.0)	REF
Secondary school	192 (84.6)	1.24[0.51-3.03]	156 (61.9)	1.56[0.84-2.89]
Vocational	13 (81.3)	0.98[0.22-4.38]	12 (60.0)	1.44[0.50-4.14]
Bachelor's degree or higher	151 (89.4)	1.89[0.73-4.92]	124 (69.7)	**2.20[1.16-4.20]**
Distance to ABTC (mins)		1.00 [.99-1.01]		0.99 [0.99-1.01]
City				
Manila City	224 (87.2)	REF	186 (64.4)	REF
Other Metro Manila Cities	150 (85.2)	0.85[0.49-1.48]	119 (62.6)	0.93[0.63-1.36]
Outside Metro Manila	15 (83.3)	0.74[0.20-2.68]	14 (66.7)	1.11[0.43-2.83]
Income (PHP)				
<5,000	17 (85.0)	REF	12 (54.6)	REF
5,000-10,000	75 (85.2)	1.02[0.26-3.97]	58 (56.9)	1.10[0.44-2.77]
10,000-15,000	86 (78.9)	0.66[0.18-2.45]	72 (55.8)	1.05[0.42-2.61]
15,000-20,000	109 (92.4)	2.14[0.53-8.69]	89 (71.2)	2.06[0.82-5.19]
>20,000	103 (88.0)	1.30[0.34-5.00]	89 (72.4)	2.18[0.86-5.52]
		1.18[0.94-1.47]		1.29[1.10-1.51]
Homeowner				

[1] REF is the reference category of comparison in the logistic regression models. The odds ratios (OR) presented are in comparison to the reference category.

No	145 (88.4)	REF	106 (60.9)	REF
Yes	245 (84.8)	0.73[0.41-1.30]	214 (65.2)	1.20[0.82-1.76]
Rent (N=172)		1.00[0.99-1.00]		1.00[0.99-1.00]
Pet owner				
No	92 (82.1)	REF	69 (55.7)	REF
Yes	298 (87.4)	1.51 [0.84-2.69]	251 (66.4)	1.58[1.04-2.38]
Pet Type				
Dog	203 (86.8)	REF	168 (64.1)	REF
Cat	55 (90.2)	1.40[0.56-3.53]	48 (71.6)	1.41[0.78-2.55]
Dog & Cat	39 (84.8)	0.85[0.35-2.07]	36 (73.5)	1.55[0.78-3.07]
Vaccinated Pet (N=380)	144 (88.3)	1.07[0.53-2.12]	123 (69.5)	1.37[0.88-2.15]
Vaccine Confidence				
Low	53 (88.3)	REF	40 (58.0)	REF
Medium	165 (89.2)	1.09[0.44-2.72]	128 (64.0)	1.28[0.74-2.25]
High	172 (82.7)	0.63[0.27-1.50]	152 (65.2)	1.36[0.79-2.36]
Rabies Exposure				
Exposure Category				
Category II	239 (86.9)	REF	198 (65.6)	REF
Category III	147 (84.5)	0.82[0.48-1.41]	118 (60.2)	0.79[0.55-1.15]
Exposure Type[†]				
Scratch	97 (85.1)	0.90[0.49-1.64]	83 (66.9)	1.20[0.78-1.85]
Bite	324 (86.2)	1.05[0.52-2.13]	263 (62.3)	0.68[0.40-1.15]
Multiple Bite	14 (77.8)	0.55[0.17-1.73]	11 (61.1)	0.89[0.34-2.34]
Exposure Site[†]				
Head & Neck	61 (87.1)	1.11[0.52-2.37]	49 (60.5)	0.85[0.52-1.38]
Arm	76 (89.4)	1.45[0.69-3.07]	54 (58.7)	0.77[0.48-1.22]
Finger	50 (79.4)	0.57[0.29-1.11]	54 (74.0)	1.74[1.00-3.04]
Torso	26 (96.3)	4.42[0.59-33.23]	22 (73.3)	1.61[0.70-3.68]
Upper leg	44 (83.0)	0.76[0.35-1.65]	39 (68.4)	1.26[0.70-2.28]
Lower Leg	145 (85.3)	0.90[0.52-1.55]	114 (61.3)	0.85[0.58-1.23]
Animal Type				
Participant Pet	230 (88.1)	REF	192 (67.6)	REF
Other's Pet	94 (83.2)	0.67[0.36-1.24]	73 (54.5)	**0.57[0.38-0.87]**
Stray	66 (83.5)	0.68[0.34-1.38]	55 (65.5)	0.91[0.54-1.52]
Animal Vaccine Status				
Vaccinated	114 (86.4)	REF	95 (66.0)	REF
Unvaccinated	190 (87.2)	1.07[0.57-2.02]	152 (61.5)	0.83[0.54-1.27]
Unknown	86 (83.5)	0.80[0.39-1.64]	73 (65.8)	0.99[0.59-1.67]
Animal Status at Day 0				
Alive	351 (86.5)	REF	287 (63.2)	REF
Dead	5 (62.5)	0.26[0.06-1.12]	5 (62.5)	0.96[0.23-4.11]
Unknown	31 (86.1)	0.97[0.36-2.61]	25 (67.6)	1.21[0.59-2.48]

[†] Multiple answers

Vaccine confidence levels are based on 10, 50, 90 percentiles.

*****Odds ratios in bold have a p-value <0.05

Individual and overall p-values are presented for categorical variables

Treatment before ABTC				
None	24 (88.9)	REF	20 (74.1)	REF
Wound washing	349 (86.0)	0.77[0.22-2.62]	288 (64.1)	0.63[0.26-1.51]
Medical consultation	12 (80.0)	0.50[0.09-2.86]	8 (42.1)	**0.25[0.07-0.89]**
Prior Vaccine				
No	317 (84.5)	REF	264 (63.3)	REF
Yes	73 (93.6)	**2.67[1.03-6.90]**	56 (65.9)	1.12[0.69-1.83]
Days to ABTC		1.10[0.96-1.27]		0.99[0.90-1.08]
Know Rabies Patient				
No	353 (86.5)	REF	289 (63.8)	REF
Yes	37 (82.2)	0.72[0.32-1.63]	31 (63.3)	0.98[0.53-1.80]
ABTC & Vaccination Experience				
Visit Duration (mins)		1.00[0.99-1.00]		0.99[0.99-1.00]
RIG				
No	276 (87.1)	REF	231 (65.4)	REF
Yes	102 (84.3)	0.80[0.44-1.44]	80 (60.2)	0.80[0.53-1.20]
Dose Awareness				
None	35 (79.6)	REF	32 (65.3)	REF
Partial	23 (88.5)	1.97[0.48-8.06]	21 (70.0)	1.24[0.47-3.30]
Full	330 (86.6)	1.66[0.76-3.66]	265 (63.0)	0.90[0.49-1.68]
ABTC Experience				
Poor experience	17 (89.5)	REF	15 (75.0)	REF
Good experience	372 (85.9)	0.72[0.16-3.18]	304 (63.2)	0.57[0.20-1.60]
Side Effect				
No	347 (85.3)	REF	268 (66.0)	REF
Yes	42 (95.5)	3.63[0.86-15.40]	32 (74.4)	1.50[0.73-3.06]

Table 6.5 shows the crude and adjusted odds ratios produced by the multivariable model. This was conducted solely with vaccine completion by self-report (N=453), as it was the primary outcome of interest. Gender and age were the only variables that maintained significance. Participants who were female (aOR 1.96, 95% CI 1.13-3.39) or aged 60+ years (aOR 5.25, 95% CI 1.14-24.09) had higher odds of vaccine completion. Education was included in the final model as it was a determined to be a confounder.

Table 6.5 Crude and adjusted odds ratios of rabies vaccine completion

Characteristics	Complete N (%)	Crude OR	P-value	Adjusted OR*	P-value
Total	390 (86.1)				
Demographics					
Gender					
Male	140 (80.5)	REF[1]	REF	REF	REF
Female	249 (89.6)	**2.09[1.22-3.57]**	**0.01**	**1.96[1.13-3.39]**	**0.02**
Respondent Age		**1.03[1.01-1.05]**	**0.01**		
16-30	124 (81.1)	REF	REF	REF	REF
31-45	139 (86.3)	1.48[0.81-2.71]	0.21	1.42[0.77-2.64]	0.26
46-59	81 (89.0)	1.89[0.88-4.10]	0.11	1.99[0.90-4.39]	0.09
60+	43 (95.6)	**5.03[1.15-21.96]**	**0.03**	**5.25[1.14-24.09]**	**0.03**
		1.03[1.01-1.05]	**0.01**		
Education					
Primary school	31 (81.6)	REF	REF	REF	REF
Secondary school	192 (84.6)	1.24[0.51-3.03]	0.64	1.64[0.63-4.28]	0.31
Vocational	13 (81.3)	0.98[0.22-4.38]	0.98	1.18[0.25-5.67]	0.84
Bachelor's degree or higher	151 (89.4)	1.89[0.73-4.92]	0.19	2.66[0.96-7.38]	0.06
Income (PHP)					
<5,000	17 (85.0)	REF	REF		
5,000-10,000	75 (85.2)	1.02[0.26-3.97]	0.98		
10,000-15,000	86 (78.9)	0.66[0.18-2.45]	0.53		
15,000-20,000	109 (92.4)	2.14[0.53-8.69]	0.29		
>20,000	103 (88.0)	1.30[0.34-5.00]	0.70		
		1.18[0.94-1.47]	0.15		
Pet Owner					
No	92 (82.1)	REF	REF		
Yes	298 (87.4)	1.51 [0.84-2.69]	0.17		
Rabies Exposure					
Exposure Category					
Category II	239 (86.9)	REF	REF		
Category III	147 (84.5)	0.82[0.48-1.41]	0.47		
Animal Type					
Participant Pet	230 (88.1)	REF	REF		
Other's Pet	94 (83.2)	0.67[0.36-1.24]	0.20		
Stray	66 (83.5)	0.68[0.34-1.38]	0.29		
Animal Status at Day 0					
Alive	351 (86.5)	REF	REF		
Dead	5 (62.5)	0.26[0.06-1.12]	0.07		
Unknown	31 (86.1)	0.97[0.36-2.61]	0.95		
Prior Vaccine					
No	317 (84.5)	REF	REF		
Yes	73 (93.6)	**2.67[1.03-6.90]**	**0.04**		

[1] REF is the reference category of comparison in the logistic regression models. The odds ratios (OR) presented are in comparison to the reference category.

ABTC & Vaccination Experience					
Dose Awareness					
None	35 (79.6)	REF	REF		
Partial	23 (88.5)	1.97[0.48-8.06]	0.79		
Full	330 (86.6)	1.66[0.76-3.66]	0.21		
ABTC Experience					
Poor experience	17 (89.5)	REF	REF		
Good experience	372 (85.9)	0.72[0.16-3.18]	0.10		
Side Effect					
No	347 (85.3)	REF	REF		
Yes	42 (95.5)	3.63[0.86-15.40]	0.08		
Odds ratios in bold have a p-value <0.05 Multivariable model includes variables with p-value <0.05 and confounding variables that changed covariate coefficients by ≥10%					

Turning to reported reasons for nonadherence. Of the participants who did not complete the vaccine schedule, 98% were aware they had to receive 4 doses. Participants were asked to provide reasons as to why they were delayed or unable to complete their vaccine schedule. The survey offered non-exclusive response options, results of which are shown in Figure 6.4. Sixty-three participants did not complete their vaccine schedules. Of these participants, the most commonly cited reasons were lack of time - 50 (79%) and travel - 30 (48%). Travel was most frequently related to the fact that Manila City residents often go to the “province” i.e. their hometowns for weekends or holidays. Two participants stated other reasons and explained further in an open-ended answer; one missed his schedule date and believed he would have to pay for the vaccine if he returned on a different date, and one lost his vaccine card and did not want to spend time going through the initial process.

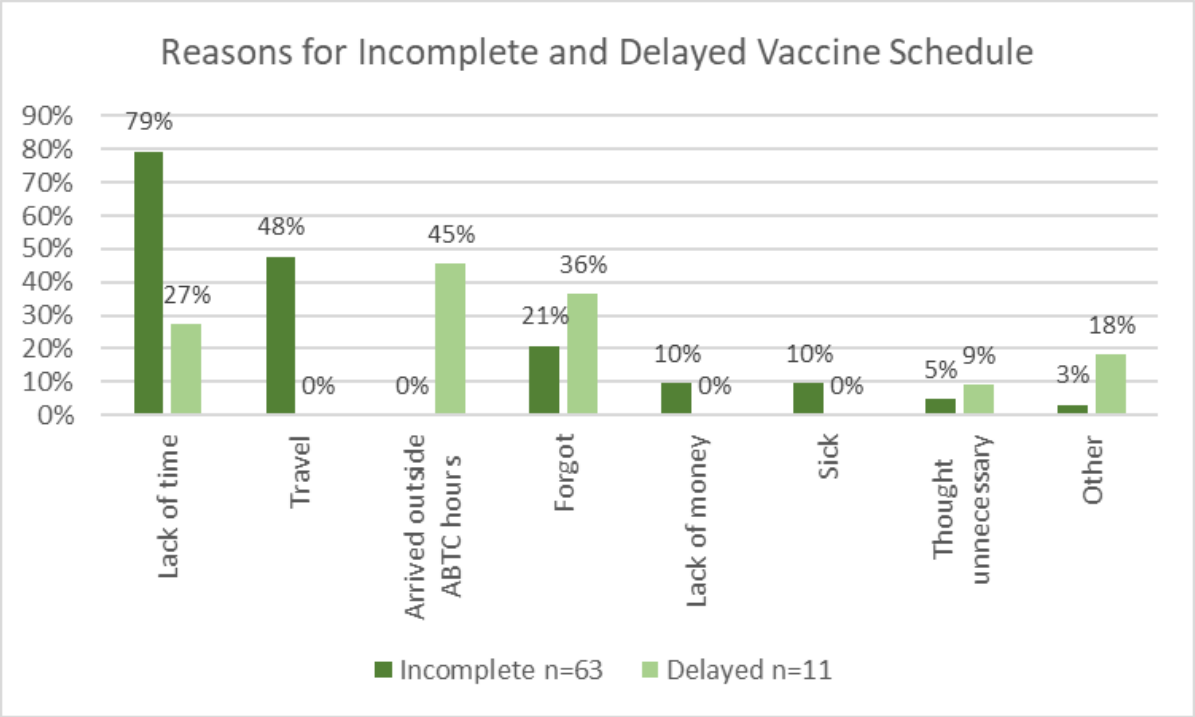


Figure 6.4 Participant reasons for incomplete and delayed vaccines

Of those who received two or more doses, 97% reported they received their vaccine on the scheduled days. Of the 11 who had delayed vaccines, the non-exclusive reasons stated for vaccine delay were; 5 arrived at SLH after ABTC hours and had to return another day, 4 forgot the schedule, 3 lacked time, and 1 thought the follow-up vaccines were unnecessary. These results are also shown in Figure 6.4. Two stated other reasons: one participant was delayed due to a miscommunication at the ABTC. They had initially returned on schedule for the second dose but received RIG only. Upon return for the third dose on day 7, the mistake was caught, and their vaccine regimen was restarted. The second participant was under COVID-19 isolation.

Discussion

Key Findings

This study showed vaccine completion of 86%, higher than published studies in the Philippines. However some of these studies did not take into account 3-dose completion by animal status [74, 241]. This completion rate is higher than the vaccine completion of 27% in the retrospective data of the SLH ABTC from 2016 to 2021.

There are various reasons for the observed higher than expected adherence. Firstly, it is possible that participants recruited into this study were more likely than the general population to complete vaccination as i) they received extra information from research assistants upon enrolment and ii) the Hawthorne effect states that subjects of a study may alter behaviour due to being observed [242]. Therefore, it is possible that study participants may have chosen to complete vaccination due to the anticipation of the follow-up call to assess vaccine status. Secondly, study recruitment occurred during a period of free vaccine provision. It was observed in a formative study at the SLH ABTC, that there are periods when vaccines were free while other times when not the case, meaning that financial assistance had to be specifically requested, elongating the process to receive free vaccines *(manuscript under preparation)*. The retrospective data did not include information on when vaccine was freely available versus paid; therefore, cost could have played a factor in those lower completion rates. It could be possible to discern if study participants had higher adherence than SLH patients in the same time period by analysing registry data of all participants who received first-dose vaccine in the ABTC during the recruitment period. However, this was not feasible as access to the data would require further ethics applications and data extraction which the study timeline could not accommodate.

A finding of interest was that, of the participants who did not complete their vaccine, 98% were aware they had to receive 4 doses, as measured in the follow-up survey. Therefore, in this study population, vaccine knowledge and awareness of the vaccine schedule did not appear to be a factor in adherence.

Participants aged 60+ had higher odds of adherence (aOR 5.25, 95% CI 1.14-24.09). The current literature shows contrasting evidence as a study in India reported that patients over the age of 60 were more likely to complete their vaccine schedule which supports this study, while a study in China reported older adults aged 55+ had higher odds of noncompletion [143, 157]. The former study hypothesized that adherence in older adults was due to the trust built between patients and their doctors as rabies vaccines were administered in the primary health care centre. In this study, the higher adherence could be explained by two factors. Firstly, at SLH, senior citizens have special queues and reduced waiting times which may significantly affect the ABTC experience. Secondly, as “lack of time” was the leading reason reported for nonadherence, the adults aged 60+ years in this study population may be without work constraints as the retirement age in the Philippines is 65 years old [243].

Female participants had higher odds of vaccine completion (aOR 1.96, 95% CI 1.13-3.39). This is supported by studies in Cambodia [160], China [157] and Bhutan [158] which also reported higher odds of completion in females.

These two results confirmed the alternative hypothesis that certain demographic factors can predict vaccine adherence outcomes with statistical significance.

To further understand vaccine adherence, participants provided reasons that caused them to discontinue vaccination. The most common reason - the biting animal was alive, is consistent with data from the study conducted in the Philippines reporting that 84% of

patients were recommended a shortened schedule due to the animal being alive after day 14 [74]. Following that, a lack of time, forgotten schedules and travel to the province are the most reported reasons for poor adherence. The first two support previous research as lack of time and work constraints were the most commonly reported reasons, reported in eight studies, and forgotten dates also commonly cited, in five studies [74, 144, 148, 150, 151, 154, 163, 167, 186, 197]. Travel to the province is a factor that may be unique to settings similar to big cities in the Philippines with customs of going to hometowns frequently, therefore similar outcomes were not clearly identified in the literature. This finding may be closely linked to the issue of access to ABTCs in rural areas as many studies have shown living in rural areas as a factor associated with poor vaccine adherence [155, 164, 165, 170]. In the 2018 study in the Philippines conducted in rural and peri-urban areas, 4% of participants stated “no knowledge of location of ABTC” as a reason for lack of initiation [74].

Cost as a barrier to vaccine uptake was reported in six studies ranging from 2% to 43% of participants [74, 144, 148, 154, 167]. As only 6% of this study’s participants reported cost as a barrier, on the lower end in comparison to other studies, it shows that the free vaccine program by the DOH may be highly important in contributing to uptake.

Hesitancy is a factor related to vaccine uptake globally [127]. In this study, vaccine confidence in both EPI vaccines and the rabies vaccine was reported to be high. However, confidence was lower for COVID-19 and dengue vaccines, the latter likely due to the dengue vaccine scare in 2017 [244]. Following the dengue vaccine scare, the Vaccine Confidence Project reported a significant drop in general vaccine confidence in the Philippines between 2015 and 2018 from 97.3% to 65.2% [176, 181]. In this study population, it appears that confidence in EPI vaccines has returned but remained low in the dengue vaccine, supporting

a 2020 study that reported similar findings [245]. An interesting finding is the lower confidence in the COVID-19 vaccine, as only 65% displayed highest confidence levels, an evident difference to confidence in rabies and EPI vaccines of 84%. These data support a study conducted in 2021 which reported COVID-19 vaccine confidence as low as 46% in the Philippines [246]. Furthermore, a response of "don't know" to the safety and effectiveness of vaccines was most frequent with COVID-19, likely linked to it being the most recent vaccine introduction.

To understand participants' relationship with their sources of information and how this could affect vaccine uptake, trust in information sources was assessed showing high confidence in doctors and lowest trust in internet and social media. The high trust in doctors in line with high vaccine confidence supports the theory that trust in healthcare providers impacts trust in vaccination [247], which acts as a facilitator to vaccine uptake. On the other hand, it is difficult to interpret the low trust in internet and social media information sources, as it encompasses a range of groups including family and friends, as well as unknown sources on the internet.

Strengths and Limitations

A major strength of this study is the prospective nature and the power to collect self-report data. Although self-report data can suffer from recall bias, retrospective studies rely on hospital registries which may be inaccurate due to either suboptimal record keeping or patients receiving follow-up doses elsewhere. The latter issue is less relevant to this study as 96% of participants reported receiving all doses at SLH. However, the 24% variance in data between the registry and self-report suggests potential recording issues. Another strength is that while prospective studies can suffer from high dropout rates, this study achieved a

follow up of 90%. This limited response bias where participants who are lost to follow up may also be the ones most likely to be nonadherent.

One limitation of this study is the age and gender demographics of the sample population in comparison to the SLH registry data. In the data from 2016-2021, 27% of ABTC patients were aged 15 and under, and male and female patients were equally represented. In this study 17% of patients were aged 16 and under, and female participants made up 62% of the study population. Therefore, there might be an underrepresentation of males and children in the study population. It is possible to speculate that children are underrepresented in the sample as guardians with children were less likely to volunteer time. This underrepresentation is a concern because vaccine uptake in younger populations is highly relevant, as a third of rabies deaths in the Philippines are in children under 15 [77].

This study attempted to assess participants' dose awareness upon enrolment, to investigate associations between knowledge and adherence. Individuals who did not have full dose awareness during the enrolment survey were provided information and reminded of the schedule. Therefore, there was likely a higher awareness as participants exited the ABTC, in comparison to the original survey-assessed knowledge. While this detracts from the ability to evaluate knowledge as a factor, it was essential to provide participants rabies information to benefit from the study.

Conclusion

Rabies vaccine completion is essential due to the fatal nature of rabies disease. 91% of participants received 3 doses indicating that with a 7-day dose schedule, improved completion is highly achievable. It is therefore important for ABTCs to use WHO prequalified vaccines to switch to a permanent 3-dose schedule.

Indirect costs from travel, and loss of productive time and wages were cited as barriers to vaccine uptake for some participants. However, vaccine costs were not a prominent factor to vaccine uptake, likely due to the provision of free vaccines in contrast to studies conducted in other countries. This suggests there is benefit in continuing to provide free vaccination.

This study also highlighted issues with ABTC access outside Manila and the National Capital Region. Evaluation of the current geographic distributions of ABTCs and the populations they serve may shed light on whether these are physical access issues such as distance and transportation costs, or lack of awareness. Thereafter, it would be important to increase awareness of the locations of ABTCs and the free services they provide.

In addition to this newly gathered evidence on rabies vaccine adherence, it is important to research factors associated with vaccine initiation, the effects of periods of paid vaccine at SLH and other ABTCs, and vaccine availability and uptake in rural areas. Further research is also necessary to understand the reasons behind higher vaccine completion in the elderly population.

6.2 Qualitative Study

Research Paper Cover Sheet

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed <u>for each</u> research paper included within a thesis.

<u>SECTION A – Student Details</u>

Student ID Number	1807686	**Title**	Ms
First Name(s)	Oladeji		
Surname/Family Name	Oloko		
Thesis Title	Factors Associated with Vaccine Uptake: A Study on Rabies Post-Exposure Prophylaxis in The Philippines		
Primary Supervisor	Chris Smith		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

<u>SECTION B – Paper already published</u>

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

<u>SECTION C – Prepared for publication, but not yet published</u>

Where is the work intended to be published?	PLOS Neglected Tropical Diseases

Please list the paper's authors in the intended authorship order:	Oladeji K Oloko, Ferdinand De Guzman, Ana R Sayo, Mary-Ann Salazar, Shuichi Suzuki, Chris Smith, Pauline Paterson
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived and designed the study, carried out data analyses and drafted the manuscript. CS and PP provided feedback and guidance for study conceptualisation and analysis. MS conducted participant recruitment. Interviews were conducted in Tagalog by MS with my guidance. All authors provided comments on the manuscript.

SECTION E

Student Signature	
Date	22/07/2023

Supervisor Signature	
Date	19/09/2023

Rabies Vaccine Uptake in the Philippines: Investigating Facilitators and Barriers to Adherence

Abstract

Rabies is endemic in the Philippines. It is a disease of public health concern with an estimated 377 deaths annually. When administered in a timely manner, a complete rabies vaccine schedule has a ninety-nine percent efficacy in disease prevention. In 2016, the Philippines Department of Health begun provision of free post-exposure vaccination at animal bite treatment centres (ABTCs) significantly reducing costs to patients. However, vaccine initiation and adherence are still suboptimal. This study, the qualitative strand of a mixed-method study, was conducted to understand the facilitators and barriers to vaccine uptake. Patients were recruited at an ABTC in Manila during their first vaccine visit and in-depth interviews were conducted with seventeen participants at the end of their vaccine schedule.

Interview transcripts were coded, and thematic analysis was conducted. The main facilitators to vaccine uptake were the influence of participants' social networks, knowledge of a rabies patient (and the associated perceived severity therein), and vaccine confidence. The main barriers were a lack of time and lost wages due to ABTC visits, inability to access ABTCs due to travel outside Manila, and the belief that vaccine completion was unnecessary. Additionally, when participants encountered delays, the fear of elongated procedures at the ABTC and reprimanding from doctors dissuaded them from returning.

This study highlighted that even when vaccines are free, indirect costs to patients are still a barrier to vaccine uptake. Furthermore, as participants were unable to complete vaccination when they travelled away from Manila, it is important to evaluate the current distribution of ABTCs across the country. An assessment of information provided to ABTC patients on

schedule delays is necessary to ensure it is not a deterrent to completion. Further research on potential interventions to increase uptake is necessary.

Introduction

Rabies vaccine, the preventative method for the most fatal infectious disease, can be administered both pre- and post-exposure. It is most commonly used in endemic settings as a post-exposure prophylaxis (PEP). Upon the onset of rabies symptoms, there are no treatment options; therefore, timely and correct administration is essential.

In 2016, the Philippines Department of Health (DOH) begun provision of free rabies vaccine at animal bite treatment centres (ABTCs) [85]. However, when there are stockouts of government supplied vaccine, patients have been required to purchase vaccines from personal funds [74]. The DOH recommends an intradermal schedule requiring doses on 3 days – Days 0, 3 & 7 when a WHO prequalified vaccine is used [95]. However, there are periodic shortages of WHO prequalified vaccines and when a non-prequalified vaccine is used, the schedule requires an additional intradermal dose on day 28, leading to a 4-visit schedule. The additional dose is due to concerns that non-prequalified vaccines are insufficiently immunogenic and may not confer complete protection with three doses [73]. The vaccine recommendation is shortened to the first 3 doses if the biting animal is still alive after 14 days, as rabies-infected canines and felines do not survive past two weeks [73].

Completion of the rabies vaccine schedule is essential as rabies deaths have been recorded in individuals who received partial vaccination [20, 109]. Therefore, it is fundamental to understand the reasons behind poor adherence to vaccine schedules to address the issues and build potential interventions. Published studies reported the most common reasons for not completing the vaccine schedule were cost, a lack of time, forgotten dates, and patients

thinking further doses were unnecessary [74, 144, 148, 150, 151, 154, 163, 167, 186, 197]. Also reported were loss of wages, the distance to the ABTC, perceived low severity of the injury, and inadequate understanding of the vaccination process [144, 145, 148, 150, 151, 154, 155, 163, 164, 167, 186]. In the Philippines, only one study identified in published literature had explored vaccine adherence since the 2016 launch of free vaccination [74]. In this 2018 study across three provinces in the Philippines, 1,111 potential exposures were reported and 45% of participants sought care. The most common reasons stated for not seeking care after an animal bite were study participants did not realise they needed PEP (37%), perceived high costs (23%), and the wound was not severe (20%). Of those who did not seek care at an ABTC, 50% practiced some home remedies ranging from wound washing, applying herbal salves or bleeding the wound, and 30% visited a tandok (traditional healer). At the ABTC, 78% of those who initiated vaccination, completed their vaccine schedules. This study reported the most common nonexclusive reasons for nonadherence as; forgotten dates (53%), costs (38%), participants thinking additional doses were unnecessary (38%), and lack of time (35%) [74].

As the rabies vaccine is different from other vaccines due to its post-exposure nature of administration, other diseases which use PEP may provide insight into issues of nonadherence. However, these were often less relevant to rabies; for example, a systematic review of HIV PEP adherence detailed stigma as a deterrent [248], while individuals reported concerns about antibiotic use in adherence studies following Anthrax attacks [249, 250]. Adverse effects of the above PEP were also reported as reasons for nonadherence which could be applicable to rabies. However, the rabies vaccine elicits only mild adverse events which may include injection site pain, headache or fever [20].

In addition to the difference in disease profiles, research has shown that immunisation perceptions can be country-, subpopulation-, or vaccine- specific [127]. However, spillover of confidence or lack of confidence, between vaccines has been found to affect immunisation attitudes [245] [181].

The facilitators and barriers to rabies vaccine uptake in the Philippines have only been explored in the 2018 study conducted in three provinces. This study, which is the qualitative strand of a mixed-method study on vaccine adherence, aims to further explore the facilitators and barriers to vaccine uptake in the Philippines, specifically in the National Capital Region.

Methods

This prospective cohort study was conducted at the San Lazaro Hospital (SLH) ABTC, located in Manila, National Capital Region (NCR). 506 participants were enrolled during their first-dose rabies vaccine visit to the ABTC, during a 2-month enrolment period from March to May 2022. Participants were screened using the following criteria and completed a Day 0 enrolment survey:

Inclusion criteria:

- Able to provide consent.
- Participant was recommended a full course of rabies post-exposure vaccination.

Exclusion criteria:

- Immunocompromised persons and those recommended a non-standard vaccine schedule.
- Minor without a consenting adult

After 30 days, all participants were called for follow up to self-report vaccine completion. *(results are reported in a manuscript of the quantitative strand of this mixed-methods*

study). A subset of the study cohort was invited to participate in in-depth interviews. Participants were to be selected for interviews using purposive sampling to build a representative sample of the initial study population in terms of age, gender, city residence, and education level. However, due to the high vaccine completion proportion in the cohort (86%), all participants who received less than 4 doses were invited for an interview, while those who completed vaccination were sampled selectively.

The interview guide was developed to understand patient experiences at the ABTC, rabies knowledge, sources of information, and the barriers and facilitators to vaccine adherence. The interviews also aimed to evaluate potential adherence interventions such as the provision of rabies information through healthcare provider communication and leaflets (already occurring at the ABTC), and the use of reminder messages. A leaflet used in the ABTC was shown to participants during the interview to determine if they had received it and to identify any impact.

Interview guides were developed to last approximately 30 minutes to prevent high research burden on participants and increase participation. Guides were developed in English, translated to Tagalog by an external translation service, adjusted by the Tagalog-native speaking study research assistant and back translated to English for quality checks. Participants had the option of the interview being conducted in either Tagalog or English. All interviews were conducted by the research assistant (MS) in Tagalog while OKO listened with a translator and provided feedback and suggested further probes. OKO has qualitative research and in-depth interview training, and extensive experience conducting interviews and focus groups. MS took qualitative methods courses and underwent in-depth interview training.

Participants received 600 PHP (£9) as compensation for time spent and to cover transport costs for returning to San Lazaro Hospital.

Interviews were audio recorded, transcribed, and translated to English. The translated transcripts were read by OKO for clarity. Where clarification was necessary, the translator listened to audio for reference and made adjustments to the translated transcripts. An inductive thematic analysis approach was used for analysis. This method was selected as thematic analysis is the most practiced method to evaluate population opinions, knowledge, and experience [191]. An inductive approach was used to capture specific facilitators and barriers, which could then be grouped into relevant themes, without preconceived researcher perspectives of reasons for vaccine adherence biasing the results. Transcripts were coded in atlas.ti [190]. Researcher OKO coded five transcripts, transcripts were read by PP & CS, codes were refined, and a codebook developed. OKO applied codes to all transcripts. A card sorting method was used to identify construct patterns and group codes into themes.

The study protocol was approved by the London School of Hygiene & Tropical Medicine (LSHTM) Research Ethics Committee (LSHTM Ethics Ref: 22718. 29/10/2021) and the San Lazaro Hospital Research Ethics Review Unit (SLH-RERU-2021-004-1) 21/01/2022).

Results

Seventeen interviews were conducted between May and June 2022, with seven participants who received four vaccine doses and ten participants who received three doses or less. Two of the ten participants received three vaccine doses and the animal of exposure was alive after fourteen days. Therefore, nine of the seventeen participants are considered to have completed their vaccination schedules according to the DOH guidelines.

Eight female and nine male participants were interviewed. Mean participant age was 31 years, ranging 19 to 49.

The results from the in-depth interviews are reported below by themes relating to the ABTC and vaccine uptake.

Animal Bite Treatment Centre Experiences

All participants reported a positive experience at the initial visit to the ABTC except one participant who thought the procedures were unclear. However, the majority of participants had a good experience and responded that they believed the process was fine and relatively fast; *"[I spent] about 2 hours, which I think is still fast for a public hospital."* (M, 22). Even if they had long and uncomfortable wait times, they considered it necessary to receive the vaccine – *"It's hot but it's okay. Worth it too."* (F, 42).

Sources of Rabies Information

Eight participants cited media and the internet as their primary source of rabies knowledge. All other participants stated either their communities as sources of information or referred to rabies disease knowledge as commonly known fact without citing a source. Of the eight, two participants had watched television programs with rabies information. An additional participant received information from a relative who had heard information from television programs.

> *"Rabies is dangerous because what we watch on TV shows, what happens to a person when they are bitten, like being afraid of wind and water."* (M, 49)

Two participants watched YouTube videos which depicted rabies patients –

> *"I don't think I know a lot. I just watched it on YouTube, like what are the things to do... Rabies is scary from what I saw on You tube, it can make you insane."* (F, 32)

Three participants stated their knowledge was from the internet, two of whom went searching for information after they were bitten, however they did not specify the websites that information was retrieved from.

> *"From the internet… It's been a long time I have known that when a dog bites you, you might really have rabies"* (F, 27)

> *"I did some research… In google… The importance of the vaccine depends on the bite. When you were bitten on the upper body, the more you need the vaccine but if it is below the body, it's not critical."* (M, 22)

One participant cited social media as their sole source of rabies information while one cited it in addition to searching the internet.

When asked what information participants received at SLH, five participants recalled the importance of vaccine completion being specifically explained to them, while twelve participants stated they received information about vaccine contraindications and side effects, but not about rabies disease or risks.

Facilitators to Vaccine Uptake

There were three facilitators to vaccine adherence that were identified; namely the influence of social networks, perceived severity linked to knowledge of a rabies patient, and vaccine confidence.

1. Influence of social networks

Many participants spoke about the influence of their social networks in relation to vaccine uptake. For all participants who completed their vaccine schedules, their family, friends, or neighbours had either advised them to seek medical care –

> *"A friend of mine told me to do so. It's better to be safe than sorry later."* (M, 39)

or where no specific advice was received, they reported that it was generally known, and the consensus amongst their communities was to seek vaccination –

"Because that's what is usually done when bitten by a dog. It's the same with my relatives; my son, my brother, my mother, my sister." (M, 45)

Even when they had encountered those that gave contradictory advice, they still pursued vaccination –

"I heard something like that too [people saying it's just a scratch, no need for vaccine]. But there's also a lot on the other side that said you should get a shot even if it is just a scratch." (F, 36)

In addition to influencing the initial decision to receive the rabies vaccine, two participants indicated their social networks influenced them into vaccine adherence, as they explicitly stated they completed their vaccine schedule as family members insisted, they do so –

"My aunt. She said I must complete the vaccine because something might happen to me."
RA: If your aunt did not force you to complete, you would not come back?
"Yes." (M, 27)

Additionally, all participants stated they would encourage any acquaintances they knew who got bitten or scratched by a dog or cat to seek vaccination.

"I will tell them to go. I was told to go to ABTC so I think I should tell them also." (M, 39)

2. Perceived severity of rabies disease

Participants discussed how their perception of the severity of rabies, which was often influenced by knowledge of a rabies patient, impacted their vaccine decision making. Three participants who received their vaccines according to the guidelines reported they knew of rabies cases in the past. One explained –

"…In our neighbourhood, somebody died like that. It was a child. A stray dog [bit him] and he only got two doses… They said he goes crazy, and saliva was

dripping, and then he died… [I completed vaccination] because the dog died. We also have experience that our neighbour died, so just to be sure. (F, 42)

One participant did not have personal experience but watched a video of a rabies patient –

"Rabies is scary from what I saw on YouTube, it can make you insane." (F, 32)

This acute knowledge and the related fear were factors in these individuals' perception of disease severity, which is important in vaccine decision making behaviours.

3. Vaccine confidence

Most participants displayed high vaccine confidence. However, one participant mentioned that he had diarrhoea after the first dose, which he thought was a side effect of vaccination and stated that it *"added to the fear"* (M, 31) of not wanting to come back for subsequent doses. However, this participant was still willing to be vaccinated and stated their main reason for incomplete vaccination was due to financial and time reasons.

Of participants who adhered to the vaccine schedule, most expressed that their belief in the benefits of vaccination reinforced their decision to complete their vaccines. Two participants specifically reported no other external facilitators, one participant simply stated they completed their vaccines *"for protection"* (M, 45). The second participant described their belief in the necessity of all vaccines not just limited to rabies, for both their children and pets –

"Even not for rabies vaccine, for my children when they are vaccinated, I make sure to complete it. That's really me and my husband with regards to the rabies vaccine, he told me you must complete that. We have a pet dog now, we are vaccinating him. (F, 32)

Further participants described how they understood the need to complete the vaccine for it to be effective and did not want to see their initial effort of getting the first vaccine wasted –

"I say, if you did not complete yet don't be assured yet." (F, 42)

"So that all my efforts are worth it. Because if I didn't complete it, it wouldn't have any effect" (F, 36)

Barriers to Vaccine Uptake

The quantitative strand of this mixed-method study reported the (nonexclusive) reasons for participants' lack of adherence *(manuscript under preparation)*.

The in-depth interviews with participants independently identified six barriers to vaccine adherence; lack of time and potential loss of wages, limited access to ABTCs, provider and clinic deterrents, misinformation from social networks, the belief that further vaccine doses were unnecessary, and extraneous circumstances specific to individuals. These barriers are presented below contextualised by the survey results where relevant.

1. Lack of time

In the quantitative study, 79% of survey participants reported a lack of time due to work or school constraints as their reason for nonadherence, the most common response. In the in-depth interviews, two participants reported work *"I have work"* (M, 39), and one participant reported school as the main reason they did not return for their vaccines –

"It was hell week at school… In hell week, a lot of papers have to be submitted." (M, 19)

This participant describes their time constraints are due to a busy period at their university which is colloquially termed "hell week".

2. Access to ABTCs

In the survey, 48% of participants stated they did not complete vaccination due to "travel to the province" during the scheduled vaccine period. Interview participants provided further insight into this as one participant explained they were unable to locate an ABTC in the area and a prohibitive cost of returning to SLH for each vaccine led to incomplete vaccination –

"We were in Laguna. We asked if there was an ABTC, there was none. We were told to go to San Lazaro… Because it's far and the transport cost. 500 pesos to Manila… If only there was money and if we didn't go home to Laguna, maybe the vaccination will be completed." (F, 47)

3. Provider and clinic deterrents

In-depth interviews captured a barrier that was not previously identified in the quantitative survey – the fear of reprimanding from doctors, increased costs, or elongated procedures due to delayed returns. This became apparent when four participants discussed encountering delays to their schedule, then deciding not to return at all due to fear of being reprimanded at the ABTC –

"I said if we go back there, they will scold us. Because it's delayed… No [I did not try to return], because I thought the doctor might be angry because we didn't go back." (F, 47)

One participant described how they were unable to return on their scheduled day due to classes, but did not consider returning to complete on a delayed schedule because they were told in the case of delays, they would have to restart the vaccine doses and would have to pay for it, in contrast to the free vaccine received at the initial visit –

"[The doctor] said, if my next vaccine is delayed, it will be back to zero again and I will pay." (M, 19)

Similarly, another participant had missed their scheduled day, this one due to arrival at the ABTC as it was closing, and they were hesitant to return because they were told they would have to pay for the following vaccines –

"I thought of coming back but in case I had to have money because they said I will have to pay for my vaccine then. I don't have enough budget then" (M, 31)

One participant disclosed they were told if they did not have their PEP card, they would have to redo the registration process and restart the vaccine schedule, they were unwilling to go through the process again and preferred to not complete vaccination –

"The issue was that the paper [PEP card] got wet. I called to ask how the process will be because of that issue. I was told to start again from the beginning." (M, 22)

4. Influence of social networks

While the influence of some participants' social networks led to vaccine completion, some participants arrived at the opposite outcome. Two participants emulated their communities, or received advice that three doses were adequate –

"I'm thinking that 3 doses is enough. So, I disregarded the fourth dose… My neighbours [told me 3 doses are okay]" (F, 27)

This opinion might be a frequent occurrence as some ABTCs in Manila City use solely the 3-dose schedule and therefore it is possible it has become common knowledge.

5. A belief that further doses were unnecessary

Some participants displayed poor understanding of the necessity of the complete vaccination schedule. This factor usually compounded an already established barrier, and was not usually the main factor in noncompletion. For example, in the case of the participant who was told they would have to restart due to a lost PEP card, when asked if he did not fear the consequence for noncompletion explained –

"I wasn't scared because at least I got the ERIG and the shots were at least three-quarters, so what I was thinking was, if the processing of the documents was a hassle, at least I had 80% of the shots." (M, 22)

Another participant was unable to return due to fear of lost wages, but felt because they had been previously vaccinated, they had adequate protection –

"I got bitten when I was young. That's why I didn't come back, because I know I have previous vaccine… I didn't know it has expiration date." (M, 27)

One participant only received two vaccine doses. While the biting animal remained alive, three vaccine doses on Days 0, 3, & 7, is the recommended guideline as animals must be

monitored for 14 days before they're considered rabies free. This participant rationalised their decision as follows –

> *"I think what is important, is that at least I have some protection from 2 doses. It's only my own theory, like now it's already 1 month passed, and the cat is still healthy. At first, I was nervous because of course I'm thinking the best interests of myself. But when I saw the cat, I see it every day. I felt relieved.*" (M, 39)

6. Extraneous circumstances

There were highly individualised issues that prevented vaccination which has been termed extraneous circumstances. Three participants were sick and unable to take themselves, or their ward to the ABTC. While one participant's house burnt down and explains why they did not return –

> *"because of continuous problems, first my son got hospitalised then there was fire, and our house was burnt."* (F, 22)

These concerns illustrate how extenuating life circumstances interfere with vaccine completion regardless of the intent to vaccinate.

Potential Adherence Interventions

Two initiatives which participants believed could improve adherence were discussed: increased provision of rabies information and schedule reminders.

1. Increased provision of rabies information using different media types at the ABTC

During their interviews, participants were shown the rabies information leaflet available at the ABTC. Eleven of the seventeen participants had not seen the leaflet during their visits to the ABTC. All participants stated they learnt valuable information from the leaflets either when seen at the ABTC or presented during the interview. One participant *"found out that rabies can cause death. It is so scary."* (F, 19). While one participant describes how the information provided can impact adherence –

"Something was written there that warns me, that I should complete the vaccine." (F, 36)

One participant commented that a video playing at the ABTC during wait times would be more effective and inclusive than a leaflet, as it would be able to serve illiterate individuals –

"This is okay, but it would be better if they explained it through video because others can't read, and it will be easier for the audience… you can only give it to those who can read it. What if "no read, no write"? What do they care about it? They will just throw it away, it's just trash" (M, 45)

2. Reminders as cues to action

The interview sought participants' opinions on the use of reminder texts or calls to aid adherence. Prior to this question, one participant unprompted expressed how a reminder they set had been essential in their return to complete the vaccine schedule –

[*gestures at mobile phone] "A reminder, it pops out, and I remember the schedule."* (M, 45)

The overwhelming majority felt a reminder could be a useful tool to improve adherence –

"It's better that someone reminds you… It's better to message them 3 days before so that they can fix their schedule before they go because they have work and can't go right away." (M, 45)

Discussion

Key Findings

The main facilitators to vaccine uptake derived from participant interviews were the influence of their social networks, their knowledge of rabies patients (and the associated perceived severity therein), and vaccine confidence. The main barriers were lack of time and lost wages due to ABTC visits, inability to access ABTCs due to travelling away from SLH, fear of doctors or procedures at ABTCs, and the belief that vaccine completion is unnecessary. Some of these facilitators and barriers are in line with the WHO SAGE Working Group Determinants of Vaccine Hesitancy's classified into the "3 Cs" [126] – Confidence, Convenience (access to ABTCs, work/school commitments) and Complacency (vaccine completion unnecessary).

Participants' social networks appeared to be a main influence on vaccine uptake, both positively and negatively, although this study reported mostly the former. Most participants discussed their network's influence in relation to vaccine initiation, but two participants indicated their communities influenced them further to complete their vaccine schedule. Only one study in a literature review of rabies vaccine uptake referenced patients' social networks or communities; Panda et al reported that 21% of participants did not complete vaccination due to ill advice from relatives or friends [151]. No studies to date have explicitly reported social norms as an influence on rabies vaccine completion.

A frequently reported reason for nonadherence in the quantitative study results was travelling outside Manila, and the associated inability to access ABTCs. As this qualitative study reported access to ABTCs as a barrier to vaccine adherence, it supports the quantitative strand. This finding is also consistent with studies which reported living in rural areas as a factor associated with poor vaccine adherence [155, 164, 165, 170].

One finding which was not discovered in the quantitative study or in the published literature is the issue surrounding fear of ABTC costs, elongated procedures, and reprimanding from doctors which dissuaded patients from returning to the ABTC. It appears that warnings made by doctors regarding timely vaccine adherence, coupled with possible paternalistic views towards the role of doctors led to some participants who would have received their vaccine on a delayed schedule, to not return at all.

The quantitative survey asked participants what sources of information they trust, reporting highest trust in doctors and lowest in media and the internet. However, where they received information from was not collected, and therefore interviews provide an interesting insight into the fact that while people might have higher confidence in doctors as a source of information, they are frequently receiving their information from media and the internet. Regarding information from the internet, it is unclear what category of websites are being used and how the information is being understood. Misinterpretation of publicly accessible research could be a danger, as the participant who stated vaccines are not critical when bitten below the trunk likely misunderstood information aiming to portray the reverse, that vaccines are more critical when bitten in the upper body.

Study's Impact on Vaccine Uptake

The quantitative strand of this study reported that 77% of participants received four or more doses, higher than the retrospective analysis of SLH data from 2016 to 2021 which showed 27% completion. Reasons for this large difference in adherence were the potential data recording issues and variable vaccine costs during certain periods. Additionally, it was theorised that study participants were more likely to complete vaccination due to increased contact with healthcare providers as the study research assistant is a qualified nurse. This

could have provided them an avenue for extra information, an opportunity to fill knowledge gaps through questions answered, and increased sense of the need to complete vaccination. This qualitative study adds evidence to this as one participant stated that the research assistant affected their decision to complete their vaccine schedule –

"I think the protection is not enough if you have just first or second doses… The one who did the interview with me for the first time [referring to research nurse] told me."
Interviewer: If you were not told that if you don't finish the vaccine, the first one is useless. Do you think you will still complete it?
"Honestly, maybe not." (F, 19)

Although only one participant explicitly stated this, the effect of the research assistant may have been an unmeasured impact on multiple participants. Further in support of this theory is the fact that when asked what information was provided at SLH, only five of seventeen participants recalled being specifically given information on the necessity of completing vaccination. Most participants stated providers gave information mainly about side effects and contraindications. Therefore, it is possible that a facilitator to vaccine adherence is increased contact with healthcare providers, which had been reported in a study conducted in India [143].

Strengths and Limitations

The choice of in-depth interviews as the method to explore vaccine uptake is a major strength of this study. The finding of participants' fear of reprimanding from doctors and ABTC procedures acting as a deterrent to vaccine adherence was due to the nature of in-depth interviews. This highlights the necessity of qualitative studies when investigating barriers and facilitators to vaccine uptake, as this issue was not reported in the quantitative survey where reasons for incomplete vaccination were sought through open-ended survey questions.

A major strength of this study is that it provided an avenue for participants who had not previously done so, to complete their vaccination as they were invited to SLH for interviews and received a travel reimbursement.

This study did not reach its target sample size. Interviews were meant to be conducted until saturation[1] was reached, estimated at 25 participants [251]. Due to the high vaccine completion rate of 86% reported in the quantitative strand of this mixed-method study, there was a low number of nonadherent participants. All participants who did not complete vaccination were invited to participate in the in-depth interviews, however only 17 interviews were conducted. It is likely that saturation was not reached in the data collected from participants with incomplete vaccine series.

A main limitation was the fact that OKO does not speak Tagalog, the language that in-depth interviews were conducted in, and therefore translators were used in the study. Context and nuance can be lost in cross-language research, and it is important to acknowledge the role of translators [252, 253]. The impact of this was attempted to be mitigated by multiple steps in the development and roll out of the study. The interview guide was drafted in English, translated to Tagalog by an external certified translator and adjusted for clarity with the research assistant. The audio recordings were then transcribed and translated by an external bilingual researcher and edited for clarity with the research assistant. The research assistant was trained in interview techniques and conducted multiple test interviews.

[1] Saturation is a criterion in qualitative research for discontinuing data collection as no additional data is likely to be found.

Conclusion

In conclusion, there are multiple factors that affect vaccine adherence and addressing them can lead to increased uptake. The finding that social networks and social norms can contribute to increased vaccine uptake suggests that there may be a possibility to leverage the influence of social norms to implement programs in barangays (equivalents of villages) that train a select group of people to become health champions. These health champions would then be able to provide accurate health information, including rabies prevention methods. Similar programs have been used to increase polio vaccine acceptance [254] and reduce vaccine hesitancy [255], most recently during COVID-19 vaccine rollout [256].

This study found that knowledge of the severity of rabies, either through in-person experience of a rabies patient, or familiarity with media portrayals, prompted vaccine adherence. This result demonstrates the importance of provision of detailed information. While healthcare providers are under immense time pressure and may be unable to counsel patients further, the use of information leaflets and videos at the ABTC may impart knowledge that could improve uptake. Studies have shown that education can have an impact on vaccine hesitancy and uptake [257]. Additionally, it is important that patients are aware of the ABTCs guidelines to prevent misconceptions and fear affecting vaccine adherence.

Recall interventions have been proven to increase patient retention [258]. If financially feasible, reminder text messages could be employed to improve vaccine adherence.

The DOH aims to establish one thousand ABTCs across the country to ensure access to rabies vaccine in close proximity to every barangay [73]. It is important to evaluate if the current distribution of ABTCs is adequately serving populations, and where they are suitably

geographically located, if their presence is being adequately published for community awareness. Furthermore, in line with the quantitative strand showing 91% of participants received 3 doses, this study supports the need to switch to a permanent 3-dose schedule using WHO prequalified vaccines as the 3-dose schedule appears to be prevailing community knowledge.

7 Study 4: Cross-Sectional Study to Characterise Failure to Initiate Rabies Vaccination

Characterising Failure to Initiate Rabies Post-Exposure Prophylaxis Vaccination

Summary

Study 4 aimed to fulfil objective 3, to characterise failure to initiate vaccination and test the hypothesis that factors such as demographics, rabies knowledge, and rabies exposure can predict vaccine initiation, however, sample size targets were not met. Three individuals who had a potential rabies exposure but did not seek PEP were surveyed. These individuals' perception of rabies risk was the key factor to lack of initiation. One participant displayed a low perceived susceptibility to rabies infection attributed to the bite being from her pet, and one participant believed a traditional method of wound bleeding was adequate. However, this sample size is insufficient to draw conclusions on population level barriers to vaccine initiation. Future recruitment for a study with similar aims could be conducted using contact tracing through the integrated bite case management (IBCM) system. IBCM is the identification of potentially rabid animals followed by contact tracing of animals and humans exposed to the index animal, and provision of post-exposure care to bite victims. This recruitment method may result in higher participant enrolment.

Introduction

This chapter focuses on a cross-sectional study aimed at characterising failure to initiate rabies vaccination in individuals who had a potential rabies exposure. Background literature on rabies epidemiology, prevention strategies, immunisation programs and vaccination schedules are covered in the thesis background, Chapter 1. In addition to understanding the factors associated with vaccine adherence covered in previous studies, initiation of rabies vaccine following an animal bite is highly important as a majority of rabies deaths do not

have any history of vaccination. A study in the Philippines reported only 10% of cases had initiated vaccination following an animal bite [233].

Globally, there are limited data on rabies vaccine initiation and adherence rates, and the factors associated with uptake. The current knowledge is summarised in Chapter 3. In the Philippines, two studies have explored this knowledge gap [74, 182]. In a 2009 study in Bohol where community members were surveyed, 74% stated a willingness to receive post-exposure prophylaxis (PEP) if they had a future rabies exposure, indicating high confidence in the rabies vaccine. Of the unwilling 26%, the most common reason for hesitancy was having no prior knowledge of PEP [182]. In a 2018 study across three provinces in the Philippines, 1,111 potential exposures were reported and 45% of participants sought care. The main reasons[1] stated for not seeking care after an animal bite were: study participants did not realise they needed PEP (38%), perceived high costs (24%), the wound was not severe (16%), the treatment centre was too far away (11%), not knowing the location of treatment centres (8%), and the treatment centre was too busy (8%) [74]. The above studies create a foundation of knowledge to address the issues surrounding rabies vaccine initiation. However, as there are limited studies, it highlights the lack of current data and the need to explore the barriers to vaccine initiation.

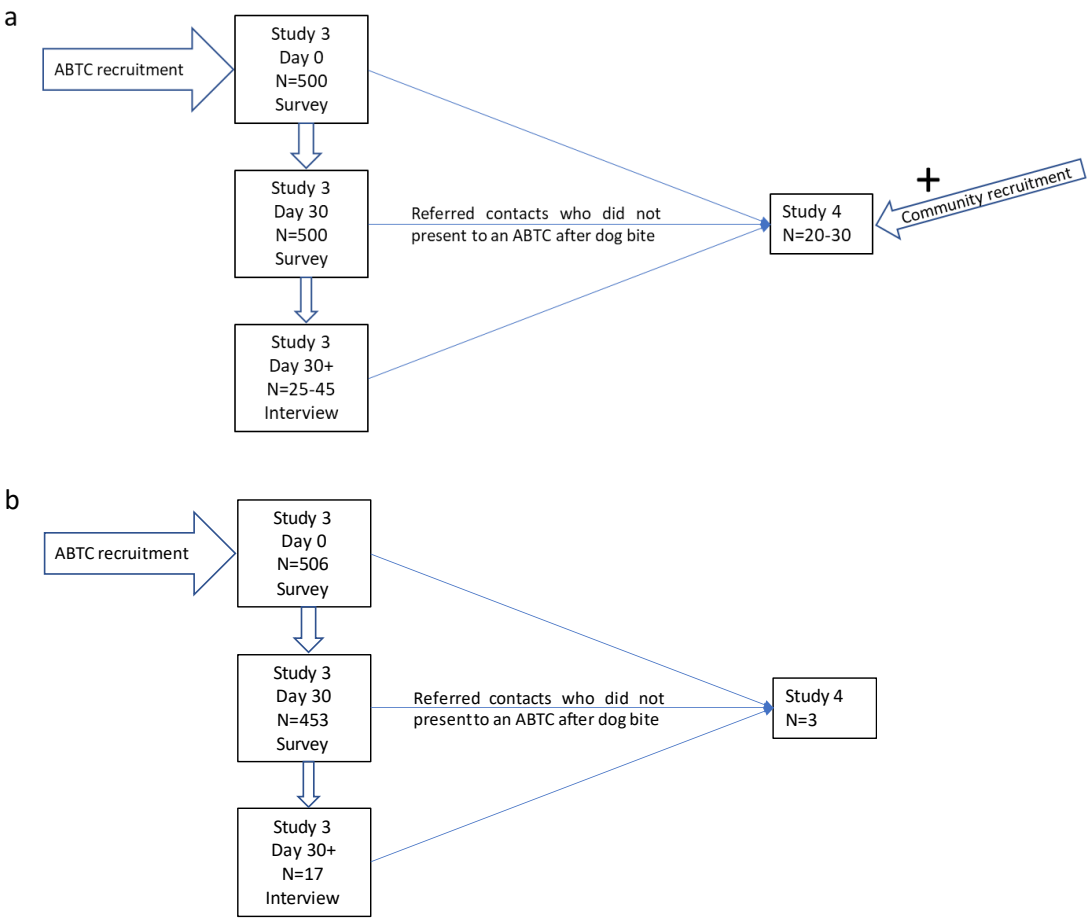
The study was designed to test the null hypothesis that factors such as demographics, vaccine confidence, rabies exposure, and knowledge, attitudes and practices cannot predict vaccine initiation, and the alternative hypothesis that these factors can predict vaccine initiation with statistical significance. The study aimed to contribute to this knowledge gap using a study population with a different demographic profile and location in the

[1] Non-exclusive answers

Philippines. Also as there are constantly changing vaccine norms and general knowledge, a more recent study is valuable.

Methods

This cross-sectional study is a sub-study of a prospective cohort that was enrolled at San Lazaro Hospital (SLH) to assess vaccine adherence. 506 prospective cohort study participants were enrolled during their first-dose rabies vaccine visit. On day 30 all participants were called for follow up and a subset of the participants participated in in-depth interviews. Snowball sampling, which is the research sampling method based on a referral system wherein participants are asked to recommend potential study participants that fit the research criteria, who then recommend further potential participants [259], was used to recruit participants for this study. During every contact with the prospective cohort study participants (initial enrolment, day 30 follow up, and interviews), and Study 4 participants themselves, participants were asked if they knew anyone who had been bitten by an animal and had not sought medical care, illustrated in Figure 7.1.



PhD Study 3 – Prospective cohort study to understand factors associated with adherence.
PhD Study 4 – Cross-sectional survey to characterise failure to initiate vaccination.

Figure 7.1 Sources of recruitment a) Planned b) Actual

If they responded affirmatively or stated they were unsure about the person's medical history, they were asked if they could refer the individual to this study. This was through a) the participant calling the contact to ascertain interest and provide consent for their phone number to be given to the study staff, or b) participant was given study phone numbers and email addresses to provide to the contact. These potential study participants were then contacted, screened for eligibility, and invited to SLH for the survey in person or the option to carry it out over the phone was offered. The following eligibility criteria was used:

Inclusion criteria:

- Individual who had a bite or scratch from a cat or dog and did not receive vaccination.

Exclusion criteria:

- Sought treatment at an ABTC but was not recommended vaccination.
- Unable to provide consent for study participation e.g. minor without a consenting adult.

When the study was initially conceptualised, eligibility criteria also required an individual to have had an animal exposure that broke skin, within the past 5 years, and had not received complete vaccination in the 3 years prior to the exposure. The requirement for an exposure that "broke skin" and individuals with no complete vaccine history within 3 years, was to include individuals that would have likely been categorised as a category II or III patient if they presented to an ABTC, i.e. those that would have been recommended vaccination. The 5-year time limit was to ensure adequate recall. Due to initial low contact referrals, these criteria were dropped to allow for more recruitment and provide familiarity for research assistants with the interview process, acting as a study pilot.

Knowledge, attitudes and practices (KAP) surveys were designed to collect data on sociodemographic characteristics, rabies exposure, accessibility to ABTCs, rabies knowledge, immunisation attitudes and vaccination practices of rabies exposed individuals. Reasons for failure to initiate and, facilitators and barriers to vaccination were collected in open-ended survey question. The questions on immunisation attitudes, and trust in healthcare providers and information sources were adapted from the Wellcome Global Monitor [237]. These questions were structured around a theoretical framework adapted from the Health Belief Model and the WHO SAGE Working Group on Vaccine Hesitancy's "3 Cs" [126]. Survey guides were developed in English, translated to Tagalog by an external translation service, adjusted by the study research assistant, and back translated to English for quality checks.

Participants had the option of the survey being conducted in either Tagalog or English. For this study all participant surveys were carried out in Tagalog by the study research assistant.

Following survey completion, study participants were provided information on rabies disease and counselled on the need to receive vaccination. As all surveys were conducted in person, it was also an opportunity for participants to receive vaccination at SLH. Participants received 500 PHP as compensation for time spent and to cover transport costs.

Study data were collected and managed using REDCap electronic data capture tools hosted at LSHTM [238-240] and analysed in Microsoft Excel [208].

The study protocol was approved by the London School of Hygiene & Tropical Medicine (LSHTM) Research Ethics Committee (LSHTM Ethics Ref: 22718. 29/10/2021) and the San Lazaro Hospital Research Ethics Review Unit (SLH-RERU-2021-004-1) 21/01/2022).

Results

Three participants were recruited. Figure 7.1 shows the planned and actual recruitment methods and numbers. Community recruitment was abandoned due to constraints of the COVID-19 pandemic. The following tables present the survey data collected from three participants. Due to the low participant numbers, the data could not be used for quantitative analyses which would assess associations to vaccine initiation, and therefore the stated hypothesis could not be tested. Therefore, the data are presented solely to report data collected, not to be interpreted or extrapolated to represent a target population. Table 7.1 shows characteristics of study participants including sociodemographic and exposure information.

Table 7.1 Characteristics of study participants

Characteristics	N
Total	3
Demographics	
Age (median)	38
Age	
<15	0
15-29	1
30-44	1
45-59	0
60+	1
Gender	
Male	1
Female	2
Education	
None	0
Primary school	0
Secondary school	1
University degree or higher	2
Income	
<5,000	0
5-10,000	1
10-15,000	2
15-20,000	0
>20,000	0
Homeowner	
Yes	3
No	0
Pet Owner	
Yes	3
No	0

Characteristics	N
Rabies Exposure	
Animal Type	
Dog	1
Cat	2
Other	0
Animal Vaccine	
Vaccinated pet	0
Unvaccinated pet	1
Unknown vaccine status pet	1
Stray	1
Animal Status	
Alive	1
Dead	0
Unknown	2
Wound Type	
Scratch	1
Bite	1
Multiple bites	1
Wound Location	
Face, neck, head	0
Arms	0
Torso	1
Leg	2
Wound treatment[†]	
None	0
Wound washing	2
Wound bleeding	1
Traditional healer	1
Prior Vaccine	
Yes	2
No	1
Distance to ABTC (median)	30 mins
Distance to ABTC	
<0.5 hours	1
0.5-1 hour	2
>1 hour	0

[†] Multiple answer options

Table 7.2 reports vaccine attitudes through perceptions of vaccine effectiveness and safety in response to the question "*For each of these vaccines, how much do you agree that vaccines are effective/safe?*". Additionally, participants were asked how strongly they agreed with the statement *"Vaccines are important for children to have"*. All participants strongly agreed.

Table 7.2 For each of these vaccines, how much do you agree that vaccines are –?

		Strongly Agree	Agree	Neither Agree or Disagree/ Don't know	Disagree	Strongly Disagree
Effective	Rabies	3	0	0	0	0
	Measles	2	1	0	0	0
	Tetanus	3	0	0	0	0
	Dengue	2	0	0	1	0
	COVID-19	2	1	0	0	0
Safe	Rabies	2	1	0	0	0
	Measles	1	2	0	0	0
	Tetanus	2	1	0	0	0
	Dengue	2	0	0	1	0
	COVID-19	2	1	0	0	0

Similarly, Table 7.3 shows trust in healthcare provider and information sources as participants respond to the question "*How much do you trust each of the following? Doctors, Scientists, the Department of Health (DOH), News Media, and Internet & Social Media*".

Table 7.3 How much do you trust each of the following?

	A Lot	Some	Not Much	Not At All	Don't know
Doctors	2	1	0	0	0
Scientists	2	0	1	0	0
DOH	2	1	0	0	0
News Media	1	0	2	0	0
Internet & Social Media	0	1	1	1	0

Table 7.4 shows reasons participants did not initiate vaccination in response to the question "*Why did you not receive a rabies vaccination after this bite?*".

Table 7.4 Responses to "Why did you not receive a rabies vaccination after this bite?"

Participant No.	Response
1.	I already have vaccine and the cat is my pet
2.	I had a hangover. I bled the wound and believed that's enough.
3.	Parents decision

Participant Profiles

Participant 1 was a 62-year-old woman. Her highest education level was a bachelor's degree, her income between 5-10,000 PHP, and a homeowner. She had pet dogs and cats, the latter of which bit her multiple times on her lower leg. The animal bite occurred a month prior to the survey, and the unvaccinated cat was still alive at the time of the survey. Following the bites, she reported that she washed the wound and did not seek vaccination as the cat was her pet and she had been previously vaccinated. She received a full course of rabies post-exposure prophylaxis 3 years prior to this exposure. Although her cat was unvaccinated, her dog had been vaccinated within the year. She classified the severity of rabies infection as "very serious" on a scale from "death" to "not serious". Regarding risk perception, she states a dog bite is "likely" to transmit rabies, "impossible" for a dog scratch, and no knowledge for bat contact. Additionally, she knew of someone who had died from rabies. She has high confidence in the safety and effectiveness of all vaccines. She reported some trust in doctors and the department of health, not much trust in scientists and the news media, and no trust at all in the internet and social media as sources of information.

Participant 2 was a 27-year-old woman. Her highest education level was secondary school, her income between 10-15,000 PHP, and a homeowner. She was bitten by a cat on her

lower leg, the vaccination and vital status of the cat was unknown as it was a stray. Following the bite, she washed and bled the wound. She did not seek vaccination primarily because she was hungover and did not wish to go to the ABTC, she also states the wound was not deep, so she believed bleeding the wound was enough, and she does not like needles. She recalls receiving a full course of rabies vaccine when she was 9 years old, which was her parent's decision. She has unvaccinated pet dogs and cats. She classified severity of rabies infection as "very serious" on a scale from "death" to "not serious". Regarding risk perception, she states a dog bite is "likely" to transmit rabies, "not likely" for a dog scratch, and no knowledge for bat contact. She does not know anyone who died from rabies. Her vaccine confidence ranged by disease. She had low confidence in the dengue vaccine, responding "disagree" to both the safety and effectiveness. She had higher confidence in other vaccines, responding "strongly agree" for rabies and tetanus, and "agree" for measles and COVID-19, for the effectiveness of vaccines and "agree" for the safety of those four vaccines. She reported "a lot" of trust in doctors, scientists, the department of health, and news media, and "some" trust in the internet and social media as a source of information.

Participant 3 was a 38-year-old man who had scratches on his upper leg and torso at age 13 from a neighbour's pet dog. The vaccination status of the dog was unknown. Following the scratch, his parents took him to the traditional healer, (Tandok/Tawak). He did not receive vaccination due to his parents' decision and has never received a rabies vaccine. Currently he earns 10-15,000 PHP, has a secondary school level education, is a homeowner, and has unvaccinated pet dogs. He has limited rabies knowledge, responding "Don't know" to questions on the severity of disease, likelihood of infection based on animal contact, and he does not know anyone who has contracted rabies. He "strongly agreed" "vaccines are important for children to have" and has high confidence in the safety and effectiveness of all

vaccines except measles for which he responds “Agree” not “strongly agree”. He reported a lot of trust in doctors, scientists, and the department of health, but not much trust in news media, and the internet and social media as sources of information.

Discussion

Factors Leading to Vaccine Initiation

While there were only three participants, some themes emerged from the responses. Participant 1’s decision not to vaccinate was based on her perception of rabies risk; she displayed a low perceived susceptibility to rabies infection which was attributed to the bite being from her pet and the prior vaccination she had received. As her pet was alive two weeks after the bite and she had received a full course of rabies vaccination within three years, this would not be considered a probable or confirmed case of rabies exposure [213], and therefore her perception of low susceptibility was likely accurate. This perception of low susceptibility due to bites from owned animals is reflected in the current literature as studies in China [174], Bhutan [158] and Ethiopia [165] have shown that people bitten by their pets have lower odds of timely vaccine uptake. However in endemic countries, pets are still a contributor to rabies transmission [59], and therefore it is important that individuals are aware that an animal bite from an unvaccinated pet is considered a potential rabies exposure.

Similar to the first participant, participant 2 based her vaccine decision making on perceived susceptibility to contracting rabies, believing that she did not need further medical care due to the shallow depth of the bite and the wound bleeding she performed. This trust in traditional preventative methods reduces the perceived benefits of vaccination as it is deemed unnecessary when bleeding the wound is carried out. In a study conducted in three

provinces across the Philippines, an average of 20% stated the severity of the wound as the reason they did not seek medical care and 4% of those who did not seek medical care bled the wound [74]. This participant identifying these factors supports the theory that individuals will build their own perceptions of their susceptibility and the benefits of vaccination through the exposure characteristics and their prior medical beliefs. Furthermore, participant 2 also showed complacency, as seeking vaccination was seen as an inconvenience not worth overcoming the fear of needles and a hangover.

Participant 3 was a child during the rabies exposure and states it was his parent's decision to not vaccinate. While there was no further data collected on the reasons behind the parent's decision in the open-ended survey question, an in-depth interview could have brought up further insight, a limitation of survey use in characterising immunisation attitudes.

Recruitment Challenges and Lessons

Of 506 participants, only 28 (5%) responded affirmatively to knowing someone who had been bitten by an animal and did not seek medical care. A potential theory for this low percentage lies in social norms, that as individuals in communities and networks mirror each other, seeking rabies immunisation following exposure has been established as the expected action, a social norm. Many studies in low and middle income countries (LMICs) have shown immunisation perceptions, whether in families, workplaces or communities, affect vaccination behaviour, positively or negatively [127]. Therefore, our study participants in the prospective cohort study who were initiating rabies vaccine are likely to know others who would also seek vaccination, leading to low opportunity for snowball sampling. Although not formally captured, as the question was not asked separately, during

conversations while the survey was ongoing, a larger proportion of participants stated they knew someone who had been bitten, however the individual had sought care.

It is likely this is not a representative population of individuals who have rabies exposures in the Philippines, as SLH is widely known in Manila. In this PhD's Study 1, during qualitative in-depth interviews, healthcare providers at SLH stated that *"Most of Filipinos are already aware of the effect of this rabies, so they would usually go to San Lazaro hospital to have their shots*". This is their perception and a reflection of the population they serve at SLH which comes from across Manila and the wider National Capital Region. Additionally, as an urban area with relatively easy access to SLH or other ABTCs, individuals may have a higher likelihood of rabies PEP initiation. This is evidenced by studies conducted in the Philippines [74], Cambodia [160] and India [175], which show increased distance to ABTC and residence in rural areas as factors associated with delay to vaccine initiation. This is further evidenced in this PhD's Study 1, as healthcare providers stated that many patients were delayed or missed their vaccine doses due to travel to the province and the inability to access ABTCs. If this study was repeated in provinces, cities, or rural areas, with less well-known or less accessible ABTCS, there could be an opportunity for increased contact referrals.

These limiting factors were considered during study conceptualisation and there was an initial plan for community recruitment. However, the COVID-19 pandemic hindered study timelines, reduced available financial resources, and limited the feasibility of setting up new study sites for community recruitment. The initial prospective study recruitment commenced on a delayed timeline and completed in May 2022 preventing opportunities to carry out community recruitment.

Further measures to include participants who did not seek vaccination were discussed. Briefly considered was the inclusion of clinically diagnosed rabies patients who did not receive rabies PEP. At SLH there was a range of 57 to 119 rabies patients per year from 2006 to 2015. Of these patients only 9.6% initiated PEP vaccination [233]. During the proposed study period, there was an ongoing study at SLH by research partners which enrolled rabies patients to trial a diagnostic tool [260]. Due to this study already in place, there would be an easily accessible target population. The ongoing study collected blood and saliva samples, and conducted a survey on rabies exposure, vaccination history and disease knowledge. This study would have added questions on factors surrounding failure to initiate vaccination, including risk and cost perceptions, vaccine hesitancy, traditional healing practices, etc. However, studies have shown that verbal autopsies cause emotional distress for respondents, as well as interviewers [261], therefore this method was decided against due to unnecessary additional burden and the possibility of causing distress and sorrow, for dying patients and their relatives. Study participants can feel they are being blamed or questioned about theirs or their loved one's decisions [262], while interviewers face challenges in deciding the right things to do and say, and the level of emotional support to offer [263, 264]. Some researchers propose these effects can be mitigated by interviewers receiving training in bereavement counselling and emotional containment strategies [265, 266], however this would not have been feasible for this study due to time and resource constraints.

For future studies, I would recommend a community approach for participant recruitment, in line with the Integrated Bite Case Management (IBCM). IBCM is the identification of potential rabid animals followed by contact tracing of animals and humans exposed to the index animal and provision of post-exposure care to bite victims [18]. Using this method to

find rabid animals and exposed individuals increases detection [267], therefore widening the study population. Furthermore, it is in line with the recommended method for rabies elimination and therefore would have practical and programmatic applicability as well as being an effective research method [18, 80].

Conclusion

This study addressed factors associated with rabies vaccine initiation. As it faced recruitment challenges the sample size is insufficient to be reflective of the target population and therefore, it is not possible to draw conclusions on population level barriers to vaccine initiation. However, the three participants responses are a useful resource, supporting prior literature and hypotheses on the effects of perception of reduced susceptibility in owned pets, trust in traditional preventative methods, and complacency, on vaccine uptake. These results indicate there is a research gap and the need for further research on the factors associated with failure to initiate rabies vaccine.

8 Discussion

This discussion chapter presents the conceptual framework informed by study results, summarises key findings by the PhD objectives they fulfilled, highlights novel observations, positions the findings in relation to existing literature, discusses strengths and limitations of the thesis overall, and reflects on the implications for future research and practice.

8.1 Summary of Findings

In order to conceptualise influences on rabies vaccine uptake, a framework was designed based on established theoretical models of behaviour change and vaccine uptake; the Health Belief Model, Betsch's determinants of vaccine decision making, and the WHO SAGE Working Group's Vaccine Hesitancy Determinants Matrix. It was first presented in Study 1 based on observations in the ABTC and healthcare providers' perspective on vaccine uptake. It has been updated with results from the further studies which reported the factors associated with vaccine adherence, and facilitators and barriers to vaccine uptake from patient perspectives. These factors are presented categorised by the groups of the WHO SAGE Working Group's Vaccine Hesitancy Determinants Matrix: individual/social group influences, clinic- and vaccine- specific issues, and contextual influences.

The framework, presented in Figure 8.1, provides a structure to understand vaccine uptake as well as a potential roadmap to select key entry points for intervention development to tackle issues of suboptimal vaccine uptake.

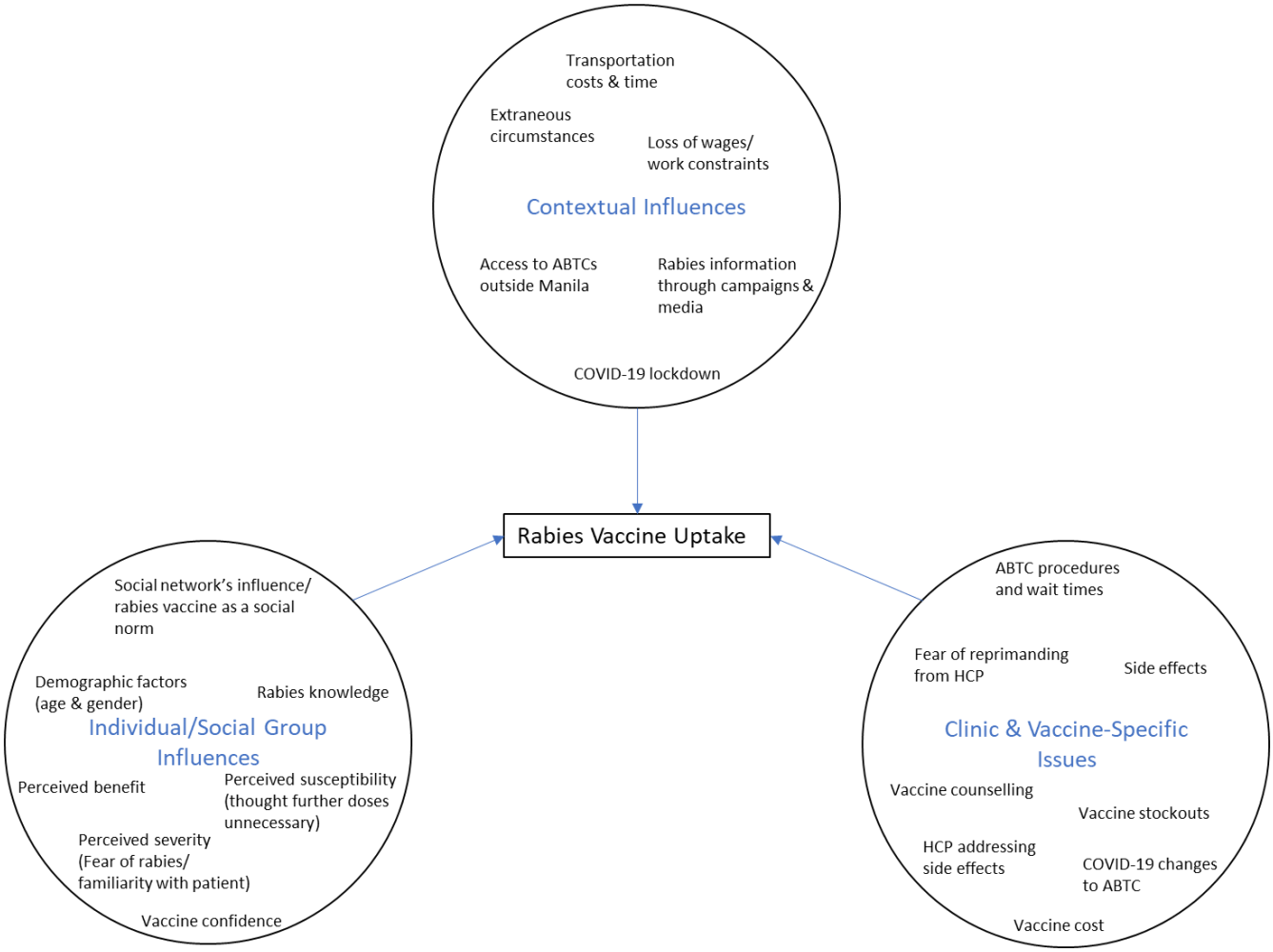


Figure 8.1 Conceptual framework of factors influencing rabies vaccine uptake. (Derived from results of PhD studies)

In the following sections I present the summary of findings by the objectives of this PhD showing how the aims were accomplished across multiple studies.

Objective 1: Exploring patient experiences in animal bite treatment centres (ABTCs).

ABTCs across the country operate in a decentralised manner under the umbrella of the local government. As such, there may be some variability in the way different ABTCs operate.

Study 1 at the San Lazaro Hospital ABTC in Manila determined that patients spent an average of 2 hours at the ABTC, and the costs varied depending on if vaccines were paid or free due to availability of government-provided vaccines, referred to as "donated" vaccines. Rabies immunoglobulin was subsidised. The total cost at the ABTC over 4 visits when vaccines were free was ₱143 (£2.50). When donated vaccines were unavailable, costs totalled ₱1,179 (£20) or ₱4,287 (£70) for intradermal (ID) or intramuscular (IM) administration respectively. Patients that required rabies immunoglobulin (RIG) paid an extra ₱2,000 (£30) or ₱6,000 (£90) for equine RIG and human RIG respectively. Financial assistance was available for everyone who needed it through the social services unit, known as the Malasakit Centre. Therefore, patients should not be hampered by the costs of immunisation. However, the different fees, procedures, and duration of visits when "donated" vaccine was not available could potentially affect patient experience and may have an impact on vaccine attitudes and adherence.

In-depth interviews in Study 3 reported that most participants had a favourable view of their experience in the ABTC and did not mind the wait times. However, four of eight participants who did not complete vaccination harboured fear of reprimanding from doctors, increased costs, or elongated procedures if they returned on a delayed schedule. The COVID-19 pandemic affected vaccine access and changed the ABTC functions from

2020. However, as no observations were carried out during the height of the pandemic in Metro Manila, it is difficult to assess the impact of the restrictive measures in place during the lockdown period in the Philippines. Post-lockdown, the only observed differences at the ABTC were requirements to use a face-shield and mask, and a change in the waiting area for vaccination from indoors to outdoors. The data in Study 2 showed a decrease in patients accessing the SLH ABTC in 2020 and 2021, the peak of the COVID-19 pandemic years. There was also a recorded rise in rabies deaths at SLH from 43 in 2019 to 65 in 2021.

Objective 2: Characterising adherence to the rabies vaccine schedule and understanding immunisation attitudes.

The retrospective analysis of over 300,000 patients at the SLH ABTC from 2016-2021 showed 27% vaccine completion of four or more doses while 54% of patients received three or more doses. The prospective study of 506 participants in 2022 showed 77% of participants received four doses and 91% received three or more doses, based on self-report. Based on the status of the animal of exposure, 86% of participants completed their vaccination schedule according to DOH guidelines.

The use of a three-dose vaccine schedule is recommended by the WHO, the shortened schedule, 7 days instead of 28, leads to vaccine completion while providing the same level of immunogenicity. At SLH, the three-dose schedule is used when WHO prequalified vaccine is available while four doses are recommended when it is not. It is possible that the use of a three-dose schedule is becoming more widely known and accepted as complete vaccination in communities leading to patients skipping the fourth dose. This is evidenced by information reported in in-depth interviews; some participants stated their neighbours commonly received three doses only, therefore, they did the same.

In the prospective data, females and older adults (60+) had increased odds of vaccine completion while the retrospective data analyses showed no statistically significant associations. The most common reasons reported for nonadherence in the Study 3 survey were a lack of time (79%) and travelling outside Manila to the province, leading to a lack of access to ABTCs (48%). Therefore, although vaccines are frequently free at the ABTC, as it was during the study duration, the incidental costs such as a loss of productive time and wages, and transportation costs are barriers to vaccine uptake.

Provider perceptions of barriers to vaccine uptake were in line with the reasons for nonadherence reported by participants. Interviews with providers in Study 1 showed they believed the most important barriers to adherence were transportation costs, work commitments and fear of wage loss, and travel to the province. Other reasons cited by providers as potential hindrances were the long lines and time-consuming procedures at the ABTC. Some participants discussed this in the Study 3 in-depth interviews as an issue that affected their experiences at the ABTC. Providers believed that vaccine costs had minimal effect on vaccine uptake, and there was low vaccine hesitancy in the ABTC patient population. It is an encouraging finding that provider perceptions of barriers to vaccine uptake were in line with those of participants as this awareness means they are more equipped to tackle issues surrounding low vaccine adherence.

A barrier to uptake discovered in the qualitative strand of Study 3 was patients' fear of reprimanding from doctors. Some study participants reported that when they encountered extraneous circumstances that led to a missed scheduled vaccine dose, they opted to not return to the ABTC on a delayed schedule as they were afraid of reprimanding from doctors. Additionally, they were informed during their first-dose visit that delays would lead to

restarting the vaccine schedule and they would then be required to pay for vaccines themselves. This unfortunate consequence of doctors aiming to ensure timely vaccine adherence led to some participants not completing their vaccine schedule.

The interviews with participants and providers identified a key facilitator of vaccine uptake, the influence of social networks and the establishment of rabies vaccination as a social norm. Conversely, individual's social networks can also have negative effects on vaccine uptake. As described above, ceasing vaccination at three doses was reported to be occasionally due to participants' communities' influence. An additional facilitator to vaccine uptake was individual's perception of the severity of rabies. It was identified through the qualitative strand of Study 3 that individuals with familiarity with a rabies patient had a perception of higher disease severity which was a facilitator of vaccine uptake. These two facilitators; influence of social network and familiarity with a rabies patient; likely interact as providers believed that the necessity of rabies vaccine was commonly known in society. Therefore, patients with preexisting understanding of the severity of rabies and the need for vaccination were more likely to access ABTCs and adhere to vaccination.

Confidence in rabies vaccines was high in this study population, an average of 84% of participants "strongly agreed" that rabies vaccines were safe and effective. This vaccine confidence was similar to that of EPI vaccines measured in this study, measles and tetanus. Study participants had lower confidence in COVID-19 and dengue vaccines, only 66% and 51%, respectively, "strongly agreed" that these vaccines were safe and effective.

Objective 3: Characterising and understanding failure to initiate rabies vaccination.

To characterise vaccine initiation, Study 4 enrolled and surveyed three individuals who had a potential rabies exposure but did not seek PEP. Although the study did not reach its target sample size it provided some insights into rabies vaccine initiation. One main takeaway from Study 4 is the impact of social networks on immunisation attitudes, and the decision to initiate vaccination. This was concluded because people who initiated vaccination had few contacts who did not. This further supports the evidence identified in Study 3 that the influence of individual's social networks is a major facilitator to vaccine uptake.

The small sample size is insufficient to draw conclusions on population level barriers to vaccine initiation. However, the participants responses showed that trust in traditional preventative methods, and individual's risk perception of rabies infection are key factors to lack of vaccine initiation. One participant believed a traditional method of wound bleeding was adequate to prevent rabies and one participant displayed a low perceived susceptibility to rabies infection attributed to the bite being from her pet. These results indicate the need for further research on the factors associated with failure to initiate rabies vaccine.

8.2 Novel Observations

This PhD identified three main novel findings:

1) Clinic and healthcare provider deterrents to vaccine adherence.

   In-depth interviews identified this barrier to vaccine adherence that had not been reported in published literature. Patients feared increased costs, elongated procedures, or being reprimanded by doctors if they returned to the ABTC on a delayed schedule to complete their vaccine series. Participants discussed encountering delays to their schedule, due to extenuating circumstances, then deciding not to return to the ABTC

due to the fear of being reprimanded, or the belief that they would be required to pay for vaccines, which would be free if they returned in a timely manner. It is not the case at SLH that patients are required to pay for their vaccines if they return on a delayed schedule. It became evident that the warnings made by doctors regarding timely vaccine adherence, coupled with possible paternalistic views towards the role of doctors, led to some participants who would have received their vaccine on a delayed schedule, to not complete vaccination at all. This is an important novel finding which can be translated into program recommendations, such as staff training to improve patient experiences and understanding, which could lead to increased vaccine adherence. The recommendation is detailed further in Section 8.6. The novelty of this finding is further highlighted as this is a recommendation which was not identified in WHO strategic frameworks or policy recommendations.

2) The influence of social networks on rabies vaccine uptake.

   The influence of social networks on vaccine uptake was identified in in-depth interviews. Participants who completed their vaccine schedules stated that their family, friends, or neighbours, had advised them to seek medical care. Even when no specific advice was received, they reported that it was generally known, and the consensus amongst their communities to seek vaccination. Therefore, the influence of social networks and the establishment of rabies vaccination as a social norm affects vaccine uptake. This is considered a novel finding as the literature review did not identify any published studies to date which explicitly reported social norms and networks as a factor related to rabies vaccine completion. This finding suggests that is a possible to leverage the influence of social norms and networks to increase vaccine uptake. Barangay (equivalents of villages) workers or members of the community could be selected and trained as vaccine

champions to provide accurate rabies prevention information and encourage community members to seek medical care following potential rabies exposures. Similar programs have been used to increase polio vaccine acceptance [254] and reduce vaccine hesitancy [255], most recently during COVID-19 vaccine rollout [256]. The influence of social networks could also be extended into social media campaigns. Statistics report that 74% of Filipinos aged 10 to 64 years-old use the internet for social media, up to 87% in children and young adults aged 10 to 30 years-old [268]. The high penetration of social media presents itself as a tool to distribute rabies vaccine information and influence vaccine uptake. Furthermore, vaccine champions can engage with wider communities online.

3) "Travelling to the province" as a major reason for poor vaccine adherence.

   Forty-eight percent of study participants cited travelling outside Manila as a reason for incomplete vaccination. Manila City residents often go to the "province" i.e. their hometowns for weekends or holidays. Participants reported a lack of access to ABTCs while in the province.

   The limited access to rabies PEP in rural areas, and the subsequent effect of lower vaccine uptake has been reported in studies globally, including in the Philippines. However, this finding can be considered novel as the phenomenon of residents of an urbanised area like Manila failing to adhere to vaccine schedules due to travelling to rural areas within the duration of their vaccine series, has not been identified in published studies. This finding reinforces the need for equitable access to ABTCs.

8.3 Relevance of Findings to Current Literature

The findings of this PhD have been contextualized in relevance to the current knowledge base in the discussion section of each study. In this section I will present the main PhD findings and how they support or diverge from current literature.

Proportion of Vaccine Completion

Study 2 retrospective analysis reported 27% vaccine completion of a four-dose schedule while Study 3 showed vaccine completion of 86% in the prospective cohort, higher than all published studies in the Philippines. A retrospective study in 2008 reported 32% vaccine completion [120] while a 2018 prospective study reported 78% [74]. Based on the significant difference in results when a retrospective study, versus prospective study, is used as the method to ascertain vaccine completion, it is likely that there is a methodological issue. This could be linked to accuracy of retrospective databases or the effects of extra contact with healthcare providers in prospective studies. Globally, rabies vaccine completion ranged from 1% in a study in India [143] to 94% in Bangladesh [144], with a median of 66% based on studies identified in the literature review search. Therefore, the results of this study fit into the landscape of vaccine completion.

Factors Associated with Vaccine Completion

This PhD reported a higher odds of rabies vaccine adherence in participants aged 60+ (OR 5.03 95% CI 1.15-21.96). The current literature shows contrasting evidence as a study in India found that patients over the age of 60 were more likely to complete their vaccine schedule which supports this study, while a study in China reported older adults aged 55+ had higher odds of noncompletion [143, 157].

Female participants also had higher odds of vaccine completion (OR 2.09 95% CI 1.22-3.57). This is supported by studies in Cambodia [160], China [157] and Bhutan [158] which reported higher odds of noncompletion in males.

Barriers and Facilitators to Uptake

Facilitators to vaccine uptake were not commonly reported in the published literature as studies focused mainly on the barriers.

The PhD studies reported that individuals' social networks appear to be a main influence on vaccine uptake, both as a facilitator and a barrier. One study referenced patients' social networks or communities; Panda et al reported that 21% of participants did not complete vaccination due to ill advice from relatives or friends [151].

The quantitative survey results reported the main barriers to vaccine adherence were a lack of time, forgotten schedules, and travel to the province. The first two support previous research as the literature review reported lack of time and work constraints as the most commonly reported reason for nonadherence, identified in eight studies, and forgotten dates also commonly cited, in five studies [74, 144, 148, 150, 151, 154, 163, 167, 186, 197].

Travel to the province is a factor that may be unique to settings similar to big cities in the Philippines with customs of going to hometowns frequently, therefore similar outcomes were not clearly identified in the literature. This finding may be closely linked to the issue of access to ABTCs in rural areas as many studies have shown living in rural areas as a factor associated with poor vaccine adherence [155, 164, 165, 170]. In the 2018 study in the Philippines conducted in rural and peri-urban areas, 4% of participants stated "no knowledge of location of ABTC" as a reason for lack of initiation [74].

Another finding which was not discovered in published literature was the fear of reprimanding from doctors for delays deterring patients from returning to the ABTC. While not specific to this exact fear dynamic, studies have established that trust in healthcare providers improves vaccine uptake [247]. In addition, a study on rabies vaccine adherence in India hypothesized that the higher of odds of vaccine completion in older adults was due to the trust built between patients and their doctors [143].

Only 6% of study participants reported vaccine costs as a barrier, on the lower end in comparison to studies across the world which reported up to 43% of participants citing vaccine cost as a barrier to uptake [74, 144, 148, 154, 167]. This shows that the free vaccine program by the DOH may be a key factor in vaccine uptake.

Vaccine Confidence and Immunisation Attitudes

In this study population, vaccine confidence in the rabies vaccine was reported to be high. This finding is consistent with the literature as general vaccine confidence has traditionally been high in the Philippines [176]. Specific to rabies vaccines, a 2009 study in Bohol, a province of the Philippines, reported 74% of study participants stated a willingness to receive PEP [182]. A 2018 community survey in three provinces across the Philippines did not uncover vaccine hesitancy except in the rare cases of pregnant women [74].

Confidence was lower for COVID-19 and dengue vaccines, the latter likely due to the dengue vaccine scare in 2017 [244]. The low COVID-19 vaccine confidence supports a study conducted in the Philippines in 2021 which reported COVID-19 vaccine confidence as low as 46% [246].

In conclusion, this PhD adds a breadth of new information to the current knowledge on rabies vaccine uptake in the Philippines, and specifically in Metro Manila where an in-depth

study had not been conducted in recent years. Healthcare contexts change regularly, illustrated by the COVID-19 pandemic and fluctuating availability of free vaccines. Therefore, it is important to continuously collect and analyse data as it sets the basis for program and policy decisions.

8.4 Strengths and Limitations

In this next section, I describe the strengths and limitations of this PhD thesis as a whole. The more detailed study-specific strengths and limitations are contained within their respective chapters.

Strengths

A major strength of this PhD is the use of multiple research methods, collecting multiple streams of data from document reviews of national guidelines, observation of patient-provider interactions, patient and provider interviews, enrolling a prospective cohort of patients, and analysis of hospital databases.

The formative observational study was used to build context of the study site, using perspectives from both healthcare providers and the patients who accessed the ABTC services. This ensured that I had a baseline understanding of the services delivered by the providers and the processes patients underwent, before delving further into patient experiences and the factors that contribute to vaccine uptake. The ABTC at SLH is unique as it is contained within a tertiary hospital, and SLH is the rabies referral centre for the National Capital Region. Additionally, ABTCs across the Philippines are likely to operate using distinct processes. Nonetheless, this formative study provided cultural sensitisation and insight into medical processes in the Philippines.

The retrospective study analysed a large dataset of over 300,000 patients which provided the vaccine completion rates over five years while the prospective study on vaccine adherence was able to build a cohort and collect more in-depth data through surveys and interviews.

The use of a qualitative study, in addition to quantitative data, in an explanatory sequential design provided an in-depth understanding of the barriers and facilitators to vaccine uptake, and the in-depth interviews uncovered themes that were not identified in the survey data.

A further strength of this PhD is the grounding in theoretical frameworks. Multiple established theories were assessed for their pertinence. The most relevant frameworks were the Health Belief Model [125], the WHO SAGE Working Group's "3 Cs" [126] and "vaccine hesitancy determinants matrix" [127], and Betsch's "determinants of vaccine decision making" [128]. These applicable frameworks were then integrated and used as a foundation to guide design of the research studies, development of data collection instruments for surveys and in-depth interviews, analysis of results, and framing of the conclusions.

San Lazaro Hospital is an excellent research environment. It has a large patient throughput providing opportunities to efficiently reach study population recruitment goals in prospective studies. During screening and enrolment for the prospective mixed-method study (Study 3), there were few rejections to participate in the study, only 1.6% of eligible patients declined. This could indicate there is high trust of research scientists and healthcare-adjacent staff, which can translate to a healthy research environment. Additionally, there has been a long-standing research partnership between Nagasaki

University and SLH which has created streamlined processes to facilitate successful research coordination.

In addition to the ease of recruitment at the ABTC, there was a low participant drop-out rate. Ninety percent of participants were reached for the Day 30+ follow-up surveys. This was achieved by using a multi-pronged system to ensure participants were being reached at their convenience. This consisted of conducting phone calls at different times of the day, including evenings and weekends, and the use of text messages to introduce and identify the study phone number to initially non-respondent participants, which was then followed by a phone call.

The multi-disciplinary research team with various expertise was fundamental to the research studies. My supervisors have expertise in vaccine confidence, vaccine uptake, decision-making and health behaviour research, and extensive knowledge of the infectious disease research landscape in the Philippines. Collaborators at SLH were the heads of the outpatient and epidemiology departments, providing knowledge into the inner workings of the ABTC. Additionally, they had extensive infectious disease and healthcare services research experience. The research assistant was a qualified nurse resident in the National Capital Region with high cultural knowledge, and quantitative and qualitative research training.

Qualitative data reporting can be highly subjective when guidelines are not in place. This thesis adhered to the COREQ reporting guideline criteria [269] which was met in reporting both qualitative studies (Study 1 and Study 3).

Limitations

As the studies were conducted in one location, the SLH ABTC, the generalisability to the Philippines as a whole is limited. There was an attempt to increase population-wide generalisability by using national data, but I was eventually unable to gain access to this data. Additionally, as the largest ABTC in the National Capital Region, the generalisability to the experiences of populations accessing smaller, local ABTCs is quite limited.

SLH is in Manila, a highly urbanised city with transport links through light rail systems, jeepneys (local buses), and tricycles. Therefore, generalisability to rural populations is limited., although some patients at the SLH ABTC were resident outside the city. In the prospective study population, 4% resided outside Metro Manila, representing the small proportion of patients that travel from rural areas further away. This is a limitation of conducting these studies at SLH, as access and immunisation attitudes may differ across the country in rural areas. This limitation is important to acknowledge as six studies identified in the literature review reported residence in urban areas as a factor associated with increased vaccine uptake, the most frequently cited factor. The difference between rural and urban populations was a consideration during study conceptualisation. There was initially an objective to recruit study participants at a rural ABTC, but this was not feasible due to restricted timelines and the impact of the COVID-19 pandemic.

The next limitation to consider is the fact that rabies deaths are primarily in individuals with animal exposures that did not initiate vaccination, as opposed to a failure to complete the vaccine schedule. A retrospective review of 2006 to 2015 data at SLH showed that of rabies deaths, 0.5% of patients reported complete vaccination, 10% had initiated PEP but had not completed the vaccine schedule, and 89.95% of rabies deaths were in patients who did not

receive any rabies PEP [233]. This PhD attempted to reach a representative sample of potentially rabies-exposed individuals who are not accessing PEP through Study 4; however, recruitment goals were unmet. The major lesson learned from this study was the need for a different recruitment method. A contact tracing community approach for participant recruitment, in line with integrated bite case management (IBCM) approach could potentially improve recruitment.

Another limitation of this PhD project is the fact that I am a foreign researcher in a country and cultural context, different from my own background and experiences. This limitation and my inability to speak Tagalog was most relevant in the qualitative studies where translators were necessary, and nuances were likely lost in the cross-language research. This limitation was acknowledged and attempts to mitigate its impact on the research studies were put into place. All studies were discussed extensively with collaborators from the Philippines at SLH. They provided input and feedback for appropriate research objectives and methods. All data collection instruments were translated to Tagalog by certified translators. The research assistant, a native Tagalog speaker, was highly integrated in the study with a deep understanding of objectives and was able to connect more with the participants as a result.

8.5 Recommendations for Further Research

Findings from this thesis suggest further research areas which should be explored and are described below:

1. Immunogenicity of the Institut Pasteur Cambodia vaccine regimen for non-WHO prequalified vaccines currently used at San Lazaro Hospital (SLH).

   The WHO prequalified vaccines have been assessed in immunogenicity studies which showed non-inferiority of the shortened "Institut Pasteur Cambodia (IPC) 2-2-2-0-0" regimen (intradermal. 7-day, 3-visit) compared to the 28-day schedules previously recommended [270]. The vaccines currently used at SLH are the non-WHO prequalified vaccines, Speeda™ [Liaoning Chengda Biology Co. Ltd] and IndiRab® [Bharat Biotech]. These vaccines have undergone safety and immunogenicity studies using the "Essen 1-1-1-1-1" (intramuscular. 28-day, 5-visit) and "Thai Red Cross 2-2-2-0-2" regimens (intradermal. 28-day, 4-visit) [271] [272]. However, there are no reported studies on the immunogenicity of these vaccines using the shortened IPC regimen. As SLH uses the Essen and Thai Red Cross schedules due to concerns that these non-WHO prequalified vaccines are insufficiently immunogenic and may not confer adequate protection using the IPC schedule, a non-inferiority study should be conducted to assess immunogenicity in the Philippines.

2. Assessment of rabies vaccine initiation and uptake in rural areas.

   Understanding factors associated with rabies vaccine initiation is key in rabies prevention as the highest rabies fatality rate is in individuals who did not receive any PEP, this is detailed in the limitations section above. Understanding failure to initiate vaccination could be investigated through a cross-sectional mixed-method study of

individuals who had a rabies exposure but did not seek medical care. The most efficient method to find study participants would be the use of contact tracing through the integrated bite case management (IBCM) system. When implemented by local animal health agencies, the IBCM system identifies and diagnoses potentially rabid animals in communities, followed by contact tracing of suspected rabid animals and human bite victims. The proportion of individuals bitten by the same dog that received rabies PEP could report the rate of vaccine initiation. A survey of enrolled participants could collect sociodemographic and rabies exposure data, analysis of which would report on categories of individuals at lower odds of vaccine initiation. In-depth interviews and focus groups could be employed to understand barriers to vaccination including exploring levels of rabies knowledge, immunisation attitudes, and ease of access to ABTCs. This information would create a foundation to develop program and policy interventions to improve vaccine initiation. As this PhD has shown, it is important to study vaccine uptake in areas considered "the province", usually less urbanised areas, as participants reported not completing vaccination when they travelled outside Manila. Therefore, it would be recommended to conduct this initiation study in a rural area. Additionally, a prospective study at a rural ABTC to assess the proportion of vaccine completion and understand vaccine adherence would contribute to increase current knowledge on vaccine adherence.

3. Analysis of nationally representative rabies epidemiological data.

   The National Rabies Information System (NaRIS) was developed by the Philippines DOH to collect patient data on individuals accessing ABTCs after a potential rabies exposure. It includes demographics, exposure history, vaccine type and doses received. The DOH encourages ABTCs across the country to use NaRIS to ensure continuous and systematic

national data collection, therefore there is a national database of rabies vaccine usage which could be analysed. Descriptive analysis of this database will provide more generalisable results to define the current proportion of vaccine completion in the Philippines. Logistic regression analyses of this large database will also help to expound on the statistically significant associations reported in this study to help develop a full picture of factors associated with vaccine uptake – do older adults and female patients have increased odds of vaccine completion nationally?

4. Evaluation of interventions to improve rabies vaccine uptake.

   This PhD has shown that there is significant room for improvement in vaccine adherence to meet country completion targets. This can be achieved by interventions designed to increase rabies vaccine uptake, however there have been no studies conducted in the Philippines to evaluate such interventions. Reminder text messages in Cote d'Ivoire and counselling in Haiti were shown to improve vaccine uptake. Results from this PhD suggest that the use of recall interventions, a variety of information provision methods, and reduced wait times at ABTCs, could be potential interventions to improve vaccine adherence. Therefore, a trial to evaluate effectiveness of these methods or other possible interventions, should be conducted. Where interventions show success and cost effectiveness, they could be translated into programs that can improve vaccine adherence and avert preventable deaths.

5. An investigation of impacts of disease outbreaks on rabies incidence and vaccine uptake.

   Data in Study 2 show a decrease in patients receiving vaccines at the SLH ABTC and an increase in rabies deaths between 2019 and 2021, during the COVID-19 pandemic. It is important to track rabies incidence to investigate if the pandemic has had a sustained

increase in deaths, and to explore the impact of disease outbreaks on vaccine uptake. This could be conducted through a time series analysis which uses historical timepoints to assess the effects of disease outbreaks and the subsequent interventions, such as lockdown measures and shifting healthcare priorities, on seeking rabies PEP and rabies deaths. Major disease outbreaks in the Philippines which could be included are the 2014 measles outbreak (November 2013 – June 2014), 2019 measles outbreak (January – April 2019), 2019 dengue outbreak (January – August 2019), and COVID-19 pandemic (January 2020 – May 2023). It would be key to take into consideration the long rabies incubation period when conducting such an analysis. In addition to investigating associations between disease outbreaks and rabies deaths, population perspectives of seeking rabies vaccine during epidemics could be investigated through focus groups.

8.6 Program and Policy Recommendations

It is essential to acknowledge the exemplary efforts the Philippines DOH has put into rabies control. The accomplishments achieved through the National Rabies Prevention and Control Program include the policies for free rabies vaccine provision, the establishment of ABTCs to increase PEP access, and education campaigns. The DOH goal is to reach 90% vaccine completion and eliminate canine-mediated human rabies by 2030 [83]. The evidence generated in this PhD thesis can be translated to program and policy recommendations targeted to specific stakeholders which can assist on the way to those goals. Some of these recommendations are in line with already proposed recommendations by the WHO and OIE, most recently in the Report of the 2015 Rabies Global Conference [189] and 2018 WHO Position Paper [95]. These include ensuring equitable access to PEP and improving surveillance and monitoring for accurate data. The use of WHO prequalified vaccines is a standing recommendation by the WHO. This PhD provides further evidence to support these recommendations within the context of the Philippines.

1. Currently, non-WHO prequalified vaccines are occasionally used at ABTCs. The policy of the DOH necessitates the use of a 28-day 4-visit vaccine schedule, when non-WHO prequalified vaccines are in use [73]. The consistent use of WHO prequalified vaccines across the Philippines will bring the national rabies program in line with the global recommendation of a 7-day 3-visit vaccine schedule. This will improve protection for patients as 91% of participants in the prospective study received three or more vaccine doses compared to 77% who received four doses. Therefore, if patients had received WHO prequalified vaccine, 91% would have been fully protected. [Stakeholder: Philippines Department of Health]

2. An evaluation of current ABTC distribution and efforts to increase access to ABTCs is crucial. A frequently reported barrier to vaccine adherence was patients travelling outside the National Capital Region and being unable to locate an ABTC. [Stakeholder: Philippines Department of Health]

3. Increasing education campaigns in communities and at ABTCs, and the use of a variety of information dissemination mediums including video, television campaigns, and social media networks. The qualitative studies indicate that patients are willing to be vaccine champions for their communities. Furthermore, training barangay workers to be health champions would leverage on the influence of social networks and provide an avenue for accurate health information to filter through communities. [Stakeholder: Philippines Department of Health]

4. An evaluation of current rabies risk exposure assessment procedures, and the provision of supplemental training on exposure assessment for medical doctors which could reduce vaccine recommendations and therefore program costs. SLH senior staff have indicated that the cost of PEP is a high operational burden. As discussed in Study 2, improved risk assessments could reduce vaccine use without compromising protection of rabies exposed patients. This supplemental training can also address the information provided during vaccine visits to ensure patients are not hesitant or failing to return due to fear of reprimanding from healthcare providers, and the misconception of free vaccine not being available when returning on a delayed schedule. [Stakeholder: Philippines Department of Health, San Lazaro Hospital, other ABTCs]

5. An assessment of data quality control in registry databases. In hospitals across the Philippines and other LMICs, patient data are occasionally maintained on paper records

which are not inputted to electronic databases. This can cause a disparity in record keeping which would not show accurate vaccine completion levels. In the prospective study, the use of both paper records and the electronic iHOMIS database was necessary to compile complete patient dataset as the latter did not contain all records. The proportion of vaccine completion in the retrospective analysis, 27%, was significantly lower than the 64% from the dataset compiled from both paper and electronic records in the prospective study, indicating there might be data entry issues. Additionally, there was a significant variance with self-report data. Therefore, a quality control assessment of electronic databases may be able to distinguish if completion rates by hospital records are accurate. [Stakeholder: Philippines Department of Health, San Lazaro Hospital, other ABTCs]

6. The use of recall interventions such as reminder phone calls or text messages to inform patients of their vaccine schedules. Recall interventions have been shown to improve vaccine uptake across many disease control programs and specifically for rabies vaccine adherence in Haiti. However, costs of such a program need to be considered. If financially feasible, the use of reminder text messages could be implemented. [Stakeholder: Philippines Department of Health, San Lazaro Hospital, other ABTCs]

8.7 Dissemination

It is essential that the results from research conducted, and the knowledge gained is disseminated across scientific networks, as well as to the relevant organisations to put the information produced into practical use. Dissemination of this PhD is being carried out through five routes:

1. Research presentations have been shared with San Lazaro Hospital staff. This was both as a method to receive feedback in co-production of the research as well as to share results.

2. Publication of manuscripts in academic journals: Studies 1 and 3 have been written for publication and will be prepared into manuscripts for submission according to journal requirements.

3. Brief reports will be developed to share with San Lazaro Hospital staff and the Philippines DOH. It will be tailored to provide key results and recommendations relevant to these organisations. This ensures that key stakeholders are aware of the research conducted and the information can be used in rabies control programs aimed at increasing vaccine uptake.

4. Summary of findings will be shared with the participants who opted in to receive results of the study they participated in.

5. Data have been presented at Nagasaki University WISE Symposium and LSHTM research meetings. Abstracts will be submitted for posters and presentations at international rabies conferences, and other conferences related to neglected tropical diseases, infectious diseases, vaccine uptake, and public health in Southeast Asia regions.

9 References

1. Fooks, A.R., *Rabies remains a 'neglected disease'.* Eurosurveillance, 2005. **10**(11): p. 1-2%P 574.

2. Jackson, A.C., *Chapter 8 - Human disease*, in *Rabies (Fourth Edition)*, A.R. Fooks and A.C. Jackson, Editors. 2020, Academic Press: Boston. p. 277-302.

3. Wunner, W.H. and K.-K. Conzelmann, *Chapter 2 - Rabies Virus*, in *Rabies (Third Edition)*, A.C. Jackson, Editor. 2013, Academic Press: Boston. p. 17-60.

4. Johnson, N., A.F. Cunningham, and A.R. Fooks, *The immune response to rabies virus infection and vaccination.* Vaccine, 2010. **28**(23): p. 3896-901.

5. Fooks, A.R., et al., *Rabies.* Nature Reviews Disease Primers, 2017. **3**(1): p. 17091.

6. Lian, M., K. Hueffer, and M.M. Weltzin, *Interactions between the rabies virus and nicotinic acetylcholine receptors: A potential role in rabies virus induced behavior modifications.* Heliyon, 2022. **8**(9): p. e10434.

7. Lentz, T.L., et al., *The acetylcholine receptor as a cellular receptor for rabies virus.* Yale J Biol Med, 1983. **56**(4): p. 315-22.

8. Hemachudha, T., et al., *Human rabies: neuropathogenesis, diagnosis, and management.* The Lancet Neurology, 2013. **12**(5): p. 498-513.

9. Thoulouze, M.I., et al., *The neural cell adhesion molecule is a receptor for rabies virus.* J Virol, 1998. **72**(9): p. 7181-90.

10. Tuffereau, C., et al., *Low-affinity nerve-growth factor receptor (P75NTR) can serve as a receptor for rabies virus.* Embo j, 1998. **17**(24): p. 7250-9.

11. Wang, J., et al., *Metabotropic glutamate receptor subtype 2 is a cellular receptor for rabies virus.* PLOS Pathogens, 2018. **14**(7): p. e1007189.

12. Shuai, L., et al., *Integrin β1 Promotes Peripheral Entry by Rabies Virus.* J Virol, 2020. **94**(2).

13. Dietzschold, B., et al., *Concepts in the pathogenesis of rabies.* Future Virology, 2008. **3**(5): p. 481-490.

14. Constantine, D.G., *Rabies transmission by nonbite route.* Public health reports (Washington, D.C. : 1896), 1962. **77**(4): p. 287-289.

15. Jackson, A.C., *Chapter 7 - Human Disease*, in *Rabies (Third Edition)*, A.C. Jackson, Editor. 2013, Academic Press: Boston. p. 269-298.

16. Anderson, L.J., et al., *Nosocomial rabies: investigation of contacts of human rabies cases associated with a corneal transplant.* American Journal of Public Health, 1984. **74**(4): p. 370-372.

17. Zhu, J.Y., J. Pan, and Y.Q. Lu, *A case report on indirect transmission of human rabies.* J Zhejiang Univ Sci B, 2015. **16**(11): p. 969-70.

18. World Health Organization (WHO). *Rabies*. 2020 [cited 2023 May 11]; Available from: https://www.who.int/news-room/fact-sheets/detail/rabies.

19. Vu, A.H., et al., *Rabies-infected dogs at slaughterhouses: A potential risk of rabies transmission via dog trading and butchering activities in Vietnam.* Zoonoses and Public Health, 2021. **68**(6): p. 630-637.

20. Rupprecht, C.E., T. Nagarajan, and H. Ertl, *Rabies Vaccines*, in *Plotkin's Vaccines*, W.A.O. Stanley A. Plotkin, Paul A. Offit, Kathryn M. Edwards, Editor. 2018, Elsevier. p. 918-942.e12.

21. Centers for Disease Control and Prevention (CDC). *Clinical Signs of Rabies in Animals*. 2011; Available from: https://www.cdc.gov/rabies/specific_groups/veterinarians/clinical_signs.html.

22. Bauerfeind, R., et al., *Zoonoses : Infectious Diseases Transmissible from Animals to Humans*. 2015, Washington, DC, UNITED STATES: ASM Press.

23. Hampson, K., et al., *Estimating the Global Burden of Endemic Canine Rabies.* PLOS Neglected Tropical Diseases, 2015. **9**(4): p. e0003709.

24. Warrell, M.J. and D.A. Warrell, *Rabies: the clinical features, management and prevention of the classic zoonosis.* Clinical Medicine, 2015. **15**(1): p. 78-81.

25. Hanlon, C.A., *Chapter 5 - Rabies in Terrestrial Animals*, in *Rabies (Third Edition)*, A.C. Jackson, Editor. 2013, Academic Press: Boston. p. 179-213.

26. Rupprecht, C.E., C.A. Hanlon, and T. Hemachudha, *Rabies re-examined.* The Lancet Infectious Diseases, 2002. **2**(6): p. 327-343.

27. Cleaveland, S., et al., *Estimating human rabies mortality in the United Republic of Tanzania from dog bite injuries.* Bull World Health Organ, 2002. **80**(4): p. 304-10.

28. Hemachudha, T., J. Laothamatas, and C.E. Rupprecht, *Human rabies: a disease of complex neuropathogenetic mechanisms and diagnostic challenges.* The Lancet Neurology, 2002. **1**(2): p. 101-109.

29. Begeman, L., et al., *Comparative pathogenesis of rabies in bats and carnivores, and implications for spillover to humans.* The Lancet Infectious Diseases, 2018. **18**(4): p. e147-e159.

30. Yousaf, M.Z., et al., *Rabies molecular virology, diagnosis, prevention and treatment.* Virology Journal, 2012. **9**(1): p. 50.

31. Warrell, D.A., *The clinical picture of rabies in man.* Transactions of the Royal Society of Tropical Medicine and Hygiene, 1976. **70**(3): p. 188-195.

32. Jackson, A.C., *Chapter 17 - Therapy of human rabies*, in *Rabies (Fourth Edition)*, A.R. Fooks and A.C. Jackson, Editors. 2020, Academic Press: Boston. p. 547-566.

33. Mallewa, M., et al., *Rabies Encephalitis in Malaria-Endemic Area, Malawi, Africa.* Emerging Infectious Diseases, 2007. **13**(1): p. 136-139.

34. Goswami, U., et al., *Psychiatric presentations in rabies. A clinico-pathologic report from South India with a review of literature.* Trop Geogr Med, 1984. **36**(1): p. 77-81.

35. de Wet, J.S., *Rabies presenting as an acute psychiatric emergency.* S Afr Med J, 1980. **58**(7): p. 297-8.

36. Burki, T., *The global fight against rabies.* The Lancet, 2008. **372**(9644): p. 1135-1136.

37. Centers for Disease Control and Prevention (CDC). *Rabies Vaccine Information Sheet*. 2013 [cited 2020 May 15]; Available from: https://www.cdc.gov/vaccines/hcp/vis/vis-statements/rabies.html.

38. Hankins, D.G. and J.A. Rosekrans, *Overview, Prevention, and Treatment of Rabies.* Mayo Clinic Proceedings, 2004. **79**(5): p. 671-676.

39. Tarantola, A., et al., *Caring for patients with rabies in developing countries - the neglected importance of palliative care.* Tropical Medicine & International Health, 2016. **21**(4): p. 564-567.

40. Jackson, A.C., et al., *Management of Rabies in Humans.* Clinical Infectious Diseases, 2003. **36**(1): p. 60-63.

41. Fooks, A.R., et al., *Current status of rabies and prospects for elimination.* Lancet, 2014. **384**(9951): p. 1389-99.

42. Hattwick, M.A.W., et al., *Recovery from Rabies.* Annals of Internal Medicine, 1972. **76**(6): p. 931-942.

43. Jackson, A.C., *Recovery from rabies: A call to arms.* Journal of the Neurological Sciences, 2014. **339**(1): p. 5-7.

44. Porras, C., et al., *Recovery from rabies in man.* Ann Intern Med, 1976. **85**(1): p. 44-8.

45. Madhusudana, S.N., et al., *Partial recovery from rabies in a six-year-old girl [2].* International Journal of Infectious Diseases, 2002. **6**(1): p. 85-86.

46. Centers for Disease Control and Prevention (CDC), *Recovery of a patient from clinical rabies--California, 2011.* MMWR Morb Mortal Wkly Rep, 2012. **61**(4): p. 61-5.

47. Gode, G.R., et al., *Treatment of 54 clinically diagnosed rabies patients with two survivals.* Indian Journal of Medical Research, 1988. **88**(6): p. 564-566.

48. Jackson, A.C., *Current and future approaches to the therapy of human rabies.* Antiviral Research, 2013. **99**(1): p. 61-67.

49. Lafon, M., *Bat rabies—the Achilles heel of a viral killer?* The Lancet, 2005. **366**(9489): p. 876-877.

50. Willoughby, R.E., et al., *Survival after Treatment of Rabies with Induction of Coma.* New England Journal of Medicine, 2005. **352**(24): p. 2508-2514.

51. Ledesma, L.A., E.R.S. Lemos, and M.A. Horta, *Comparing clinical protocols for the treatment of human rabies: the Milwaukee protocol and the Brazilian protocol (Recife).* Rev Soc Bras Med Trop, 2020. **53**: p. e20200352.

52. Zeiler, F.A. and A.C. Jackson, *Critical Appraisal of the Milwaukee Protocol for Rabies: This Failed Approach Should Be Abandoned.* Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques, 2016. **43**(1): p. 44-51.

53. Hunter, M., et al., *Immunovirological correlates in human rabies treated with therapeutic coma.* Journal of Medical Virology, 2010. **82**(7): p. 1255-1265.

54. Van Thiel, P.-P.A.M., et al., *Fatal Human Rabies due to Duvenhage Virus from a Bat in Kenya: Failure of Treatment with Coma-Induction, Ketamine, and Antiviral Drugs.* PLoS Neglected Tropical Diseases, 2009. **3**(7): p. e428.

55. Aramburo, A., et al., *Failure of the Milwaukee Protocol in a Child With Rabies.* Clinical Infectious Diseases, 2011. **53**(6): p. 572-574.

56. Hemachudha, T., et al., *Failure of therapeutic coma and ketamine for therapy of human rabies.* Journal of NeuroVirology, 2006. **12**(5): p. 407-409.

57. Jochmans, D. and J. Neyts, *The path towards effective antivirals against rabies.* Vaccine, 2019. **37**(33): p. 4660-4662.

58. Banyard, A.C., et al., *Re-evaluating the effect of Favipiravir treatment on rabies virus infection.* Vaccine, 2019. **37**(33): p. 4686-4693.

59. Taylor, L.H., et al., *Difficulties in estimating the human burden of canine rabies.* Acta Tropica, 2015. **165**: p. 133-140.

60. Fitzpatrick, M.C., et al., *Cost-Effectiveness of Canine Vaccination to Prevent Human Rabies in Rural Tanzania.* Annals of Internal Medicine, 2014. **160**(2): p. 91-100.

61. Wallace, R.M. and J. Blanton, *Chapter 4 - Epidemiology*, in *Rabies (Fourth Edition)*, A.R. Fooks and A.C. Jackson, Editors. 2020, Academic Press: Boston. p. 103-142.

62. World Health Organization (WHO). *Animal Bites*. 2018 [cited 2020 May 15]; Available from: https://www.who.int/news-room/fact-sheets/detail/animal-bites.

63. Hampson, K., et al., *Transmission dynamics and prospects for the elimination of canine rabies.* PLoS Biol, 2009. **7**(3): p. e53.

64. Coleman, P.G. and C. Dye, *Immunization coverage required to prevent outbreaks of dog rabies.* Vaccine, 1996. **14**(3): p. 185-6.

65. Morters, M.K., et al., *Achieving Population-Level Immunity to Rabies in Free-Roaming Dogs in Africa and Asia.* PLOS Neglected Tropical Diseases, 2014. **8**(11): p. e3160.

66. Taylor, L.H., et al., *The Role of Dog Population Management in Rabies Elimination-A Review of Current Approaches and Future Opportunities.* Front Vet Sci, 2017. **4**: p. 109.

67. Shwiff, S., K. Hampson, and A. Anderson, *Potential economic benefits of eliminating canine rabies.* Antiviral Research, 2013. **98**(2): p. 352-356.

68. Tohma, K., et al., *Phylogeographic analysis of rabies viruses in the Philippines.* Infection, Genetics and Evolution, 2014. **23**: p. 86-94.

69. Dela Cruz, A.R.D., *Dogs, Rabies and the Filipinos: The Anti-Rabies Campaign in the Philippines, 1910-1934*, in *DLSU Research Congress 2019*. 2019: Manila, Philippines.

70. Institute for Health Metrics and Evaluation (IHME). *GBD Compare*. 2019 [cited 2023 August 10]; Available from: https://vizhub.healthdata.org/gbd-compare/.

71. Department of Health Philippines, *2018 Rabies Surveillance*, E. Bureau, Editor. 2018: Manila, Philippines.

72. Philippines Statistics Authority, *Updated Population Projections Based on the Results of 2015 POPCEN*. 2019: Manila, Philippines.

73. Department of Health Philippines, *National Rabies Prevention and Control Program - Manual of Procedures (2019)*. 2019: Manila, Philippines.

74. Amparo, A.C.B., et al., *The evaluation of Animal Bite Treatment Centers in the Philippines from a patient perspective.* PLOS ONE, 2018. **13**(7): p. e0200873.

75. Rakuten Insight. *Pet Ownership in Asia*. 2021 27 February 2021 [cited 2023; Available from: https://insight.rakuten.com/pet-ownership-in-asia/.

76. Dizon, T.J.R., et al., *Household survey on owned dog population and rabies knowledge in selected municipalities in Bulacan, Philippines: A cross-sectional study.* PLoS Negl Trop Dis, 2022. **16**(1): p. e0009948.

77. WHO Western Pacific Region (WPRO). *Rabies in the Philippines*. 2019 [cited 2019 November 5]; Available from: http://www.wpro.who.int/philippines/areas/communicable_diseases/rabies/continuation_rabies_area_page/en/.

78. Amparo, A.C.B., et al., *The evaluation of operating Animal Bite Treatment Centers in the Philippines from a health provider perspective.* PLOS ONE, 2018. **13**(7): p. e0199186.

79. Department of Health Philippines. *Rabies Prevention and Control Program*. 2019 [cited 2019 November 5]; Available from: https://www.doh.gov.ph/national-rabies-prevention-and-control-program.

80. O'Brien, K.L. and T. Nolan, *The WHO position on rabies immunization – 2018 updates.* Vaccine, 2019. **37**: p. A85-A87.

81. Deray, R., et al., *Protecting children from rabies with education and pre-exposure prophylaxis: A school-based campaign in El Nido, Palawan, Philippines.* PLOS ONE, 2018. **13**(1): p. e0189596.

82. Sreenivasan, N., et al., *Overview of rabies post-exposure prophylaxis access, procurement and distribution in selected countries in Asia and Africa, 2017–2018.* Vaccine, 2019. **37**: p. A6-A13.

83. Department of Health Philippines, D.o.A.B.o.A.I., *National Rabies Prevention and Control Program - Strategic Plan 2020-2025*. 2020: Manila, Philippines.

84. Conan, A., et al., *Population Dynamics of Owned, Free-Roaming Dogs: Implications for Rabies Control.* PLoS Negl Trop Dis, 2015. **9**(11): p. e0004177.

85. Government of the Republic of the Philippines, *Free anti-rabies vaccines in 2016*, in *Official Gazette*. 2016, Presidential Communications Operations Office (PCOO): Manila, Philippines.

86. Dreesen, D.W., *A global review of rabies vaccines for human use.* Vaccine, 1997. **15**: p. S2-S6.

87. Tarantola, A., *Four Thousand Years of Concepts Relating to Rabies in Animals and Humans, Its Prevention and Its Cure.* Tropical Medicine and Infectious Disease, 2017. **2**(2): p. 5.

88. Moore, S.M., C.R. Gordon, and C.A. Hanlon, *Chapter 12 - Measures of Rabies Immunity*, in *Rabies (Third Edition)*, A.C. Jackson, Editor. 2013, Academic Press: Boston. p. 461-495.

89. World Health Organization (WHO), *Rabies Vaccines WHO Position Paper.* Weekly Epidemiological Record= Relevé épidémiologique hebdomadaire, 2007. **82**(49-50): p. 425-435.

90. Warrell, M.J., *Rabies post-exposure vaccination in 2 visits within a week: A 4-site intradermal regimen.* Vaccine, 2019. **37**(9): p. 1131-1136.

91. World Health Organization (WHO). *Prequalified Vaccines*. WHO - Prequalification of Medical Products (IVDs, Medicines, Vaccines and Immunization Devices, Vector Control) 2023 18/05/2023]; Available from: https://extranet.who.int/pqweb/vaccines/prequalified-vaccines.

92. Salahuddin, N., M.A. Gohar, and N. Baig-Ansari, *Reducing Cost of Rabies Post Exposure Prophylaxis: Experience of a Tertiary Care Hospital in Pakistan.* PLOS Neglected Tropical Diseases, 2016. **10**(2): p. e0004448.

93. Gongal, G. and G. Sampath, *Introduction of intradermal rabies vaccination – A paradigm shift in improving post-exposure prophylaxis in Asia.* Vaccine, 2019. **37**: p. A94-A98.

94. Denis, M., et al., *An overview of the immunogenicity and effectiveness of current human rabies vaccines administered by intradermal route.* Vaccine, 2019. **37**: p. A99-A106.

95. World Health Organization (WHO), *Rabies vaccines: WHO position paper, April 2018 – Recommendations.* Vaccine, 2018. **36**(37): p. 5500-5503.

96. Fooks, A.R., A.C. Banyard, and H.C.J. Ertl, *New human rabies vaccines in the pipeline.* Vaccine, 2019. **37**: p. A140-A145.

97. Jenkin, D., et al., *Safety and immunogenicity of a simian-adenovirus-vectored rabies vaccine: an open-label, non-randomised, dose-escalation, first-in-human, single-centre, phase 1 clinical trial.* Lancet Microbe, 2022. **3**(9): p. e663-e671.

98. Kessels, J.A., et al., *Pre-exposure rabies prophylaxis: a systematic review.* Bulletin of the World Health Organization, 2017. **95**(3): p. 210-219C.

99. Chulasugandha, P., et al., *Cost comparison of rabies pre-exposure vaccination with post-exposure treatment in Thai children.* Vaccine, 2006. **24**(9): p. 1478-1482.

100. Quiambao, B., et al., *Health economic assessment of a rabies pre-exposure prophylaxis program compared with post-exposure prophylaxis alone in high-risk age groups in the Philippines.* International Journal of Infectious Diseases, 2020. **97**: p. 38-46.

101. Fooks, A.R., et al., *Development of a multivalent paediatric human vaccine for rabies virus in combination with Measles–Mumps–Rubella (MMR).* Vaccine, 2014. **32**(18): p. 2020-2021.

102. Both, L., et al., *Passive immunity in the prevention of rabies.* The Lancet Infectious Diseases, 2012. **12**(5): p. 397-407.

103. Kang, G., et al., *Active safety surveillance of rabies monoclonal antibody and rabies vaccine in patients with category III potential rabies exposure.* The Lancet Regional Health - Southeast Asia, 2023. **14**.

104. Sparrow, E., et al., *Recent advances in the development of monoclonal antibodies for rabies post exposure prophylaxis: A review of the current status of the clinical development pipeline.* Vaccine, 2019. **37**: p. A132-A139.

105. Müller, T., et al., *Correction: Development of a Mouse Monoclonal Antibody Cocktail for Post-exposure Rabies Prophylaxis in Humans.* PLOS Neglected Tropical Diseases, 2009. **3**(11): p. 10.1371/annotation/df98339d-6bdb-40ed-af83-cc38b249264a.

106. Beck, A., et al., *Strategies and challenges for the next generation of therapeutic antibodies.* Nature Reviews Immunology, 2010. **10**(5): p. 345-352.

107. Girard, L.S., et al., *Expression of a human anti-rabies virus monoclonal antibody in tobacco cell culture.* Biochemical and Biophysical Research Communications, 2006. **345**(2): p. 602-607.

108. Fayaz, A., et al., *Antibody persistence, 32 years after post-exposure prophylaxis with human diploid cell rabies vaccine (HDCV).* Vaccine, 2011. **29**(21): p. 3742-5.

109. Rupprecht, C.E., et al., *Evidence for a 4-dose vaccine schedule for human rabies post-exposure prophylaxis in previously non-vaccinated individuals.* Vaccine, 2009. **27**(51): p. 7141-7148.

110. Kumar, S.K., P. Gupta, and P.K. Panda, *Death from rabies: The reason being poor compliance to vaccination or it's failure.* J Family Med Prim Care, 2020. **9**(8): p. 4437-4440.

111. Wilde, H., *Failures of post-exposure rabies prophylaxis.* Vaccine, 2007. **25**(44): p. 7605-7609.

112. Tinsa, F., et al., *Rabies encephalitis in a child: a failure of rabies post exposure prophylaxis?* BMJ Case Rep, 2015. **2015**.

113. Shantavasinkul, P., et al., *Failure of Rabies Postexposure Prophylaxis In Patients Presenting with Unusual Manifestations.* Clinical Infectious Diseases, 2010. **50**(1): p. 77-79.

114. Biogenetech. *VINRAB*. 2023 18/05/2023]; Available from: https://www.biogenetech.co.th/products/vinrab/.

115. Bharat Serums and Vaccines Limited (BSV). *Emergency Medicine*. 2023; Available from: https://bsvgroup.com/products/emergency/.

116. Walpole, S.C., et al., *The weight of nations: an estimation of adult human biomass.* BMC Public Health, 2012. **12**: p. 439.

117. World Health Organization (WHO). *Falsified Rabies Vaccines and Anti-Rabies Serum Circulating in the Philippines*. Medical Product Alert 2019 [cited 2019 October 30]; Available from: https://www.who.int/medicines/publications/drugalerts/drug_alert-8-2019/en/.

118. Henson, K.E.R., A.A.C. Santiago, and S.S. Namqui, *Counterfeit Rabies Vaccines: The Philippine Experience.* Open Forum Infectious Diseases, 2020. **7**(8).

119. Taylor, E., et al., *Avoiding preventable deaths: The scourge of counterfeit rabies vaccines.* Vaccine, 2019. **37**(17): p. 2285-2287.

120. Quiambao, B.P., et al., *Rabies Post-Exposure Prophylaxis in the Philippines: Health Status of Patients Having Received Purified Equine F(ab')2 Fragment Rabies Immunoglobulin (Favirab).* PLoS Neglected Tropical Diseases, 2008. **2**(5): p. e243.

121. Phillips, D.E., et al., *Determinants of effective vaccine coverage in low and middle-income countries: a systematic review and interpretive synthesis.* BMC Health Services Research, 2017. **17**(1).

122. Dreibelbis, R., et al., *The Integrated Behavioural Model for Water, Sanitation, and Hygiene: a systematic review of behavioural models and a framework for designing and evaluating behaviour change interventions in infrastructure-restricted settings.* BMC Public Health, 2013. **13**(1): p. 1015.

123. Sirur, R., et al., *The role of theory in increasing adherence to prescribed practice.* Physiotherapy Canada. Physiotherapie Canada, 2009. **61**(2): p. 68-77.

124. Munro, S.A., et al., *Patient Adherence to Tuberculosis Treatment: A Systematic Review of Qualitative Research.* PLOS Medicine, 2007. **4**(7): p. e238.

125. Champion, V.L. and C.S. Skinner, *The Health Belief Model*, in *Health Behavior and Health Education: Theory, Research, and Practice*. 2008, Jossey-Bass: San Francisco, CA, US. p. 45-65.

126. MacDonald, N.E., *Vaccine hesitancy: Definition, scope and determinants.* Vaccine, 2015. **33**(34): p. 4161-4164.

127. Larson, H.J., et al., *Understanding vaccine hesitancy around vaccines and vaccination from a global perspective: A systematic review of published literature, 2007–2012.* Vaccine, 2014. **32**(19): p. 2150-2159.

128. Betsch, C., R. Böhm, and G.B. Chapman, *Using Behavioral Insights to Increase Vaccination Policy Effectiveness.* Policy Insights from the Behavioral and Brain Sciences, 2015. **2**(1): p. 61-73.

129. Janz, N.K. and M.H. Becker, *The Health Belief Model: A Decade Later.* Health Education Quarterly, 1984. **11**(1): p. 1-47.

130. Coe, A.B., et al., *The use of the health belief model to assess predictors of intent to receive the novel (2009) H1N1 influenza vaccine.* INNOVATIONS in pharmacy, 2012. **3**(2).

131. Isagani, D., *Administrative Map of the Philippines*. 2019: CC BY-SA 4.0.

132. Olanday, D. and J. Rigby, *Inside the world's longest and strictest coronavirus lockdown in the Philippines*, in *The Telegraph*. 2020.

133. Bracci, L., et al., *Molecular mimicry between the rabies virus glycoprotein and human immunodeficiency virus-1 GP120: cross-reacting antibodies induced by rabies vaccination.* Blood, 1997. **90**(9): p. 3623-8.

134. Bahmanyar, M., et al., *Successful protection of humans exposed to rabies infection. Postexposure treatment with the new human diploid cell rabies vaccine and antirabies serum.* Jama, 1976. **236**(24): p. 2751-4.

135. Wilde, H., et al., *Efficacy study of a new albumin-free human diploid cell rabies vaccine (Lyssavac-HDC, Berna) in 100 severely rabies-exposed Thai patients.* Vaccine, 1995. **13**(6): p. 593-6.

136. Sudarshan, M.K., et al., *An immunogenicity, safety and post-marketing surveillance of a novel adsorbed human diploid cell rabies vaccine (Rabivax) in Indian subjects.* Hum Vaccin, 2008. **4**(4): p. 275-9.

137. Wilde, H., et al., *Worldwide rabies deaths prevention—A focus on the current inadequacies in postexposure prophylaxis of animal bite victims.* Vaccine, 2016. **34**(2): p. 187-189.

138. Brown, D., et al., *Intradermal pre-exposure rabies vaccine elicits long lasting immunity.* Vaccine, 2008. **26**(31): p. 3909-12.

139. Brown, D., A.R. Fooks, and M. Schweiger, *Using intradermal rabies vaccine to boost immunity in people with low rabies antibody levels.* Adv Prev Med, 2011. **2011**: p. 601789.

140. Warrell, M.J., et al., *A simplified 4-site economical intradermal post-exposure rabies vaccine regimen: a randomised controlled comparison with standard methods.* PLoS Negl Trop Dis, 2008. **2**(4): p. e224.

141. Department of Health Philippines, *National Rabies Prevention and Control Program - Manual of Operations (2012)*. 2012: Manila, Philippines.

142. World Health Organisation (WHO). *The Global Health Observatory - Rabies*. 2023 [cited 2023 20/05/2023]; Available from: https://www.who.int/data/gho/data/themes/topics/rabies.

143. Gadapani, B., S. Rahini, and R.M. Manapurath, *Noncompliance of the postexposure prophylactic vaccination following animal bites reporting to a rural primary health center.* J Family Med Prim Care, 2019. **8**(10): p. 3258-3262.

144. Alam, A.N., M. Siddiqua, and J. Casal, *Knowledge and attitudes about rabies in dog-bite victims in Bangladesh.* One Health, 2020. **9**: p. 100126.

145. Haradanhalli, R.S., et al., *Health-seeking behavior and compliance to post exposure prophylaxis among animal bite victims in India.* Indian J Public Health, 2019. **63**(Supplement): p. S20-s25.

146. Mankeshwar, R., V. Silvanus, and S. Akarte, *Evaluation of intradermal vaccination at the anti rabies vaccination OPD.* Nepal Med Coll J, 2014. **16**(1): p. 68-71.

147. Ramesh Masthi, N.R., B.S. Pradeep, and G. Bilagumba, *A multicentric community survey on animal exposures among humans in India.* Indian J Public Health, 2019. **63**(Supplement): p. S9-s14.

148. Shankaraiah, R.H., et al., *Compliance to anti-rabies vaccination in post-exposure prophylaxis.* Indian J Public Health, 2015. **59**(1): p. 58-60.

149. *Rabies vaccines. WHO position paper.* Wkly Epidemiol Rec, 2007. **82**(49-50): p. 425-35.

150. Pal, R., et al., *Compliance rate of anti-rabies vaccination in patients presenting with an animal bite.* International Journal of Academic Medicine, 2022. **8**(4): p. 199-204.

151. Panda, M. and R. Kapoor, *Compliance to post-exposure prophylaxis among animal bite patients – A hospital-based epidemiological study.* Journal of Family Medicine and Primary Care, 2022. **11**(10).

152. Zamina, B.Y.G., et al., *[Influence of the knowledge of patients consulting at the Treichville antirabies Center on adherence to post-exposure prophylaxis].* Rev Epidemiol Sante Publique, 2019. **67**(2): p. 92-97.

153. Tiembré, I., et al., *[Adherence to rabies vaccine treatment for people exposed to rabies in Abidjan (Côte d' Ivoire)].* Sante Publique, 2009. **21**(6): p. 595-603.

154. Tiembre, I., et al., *Abandons de prophylaxie post-exposition au Centre antirabique d'Abidjan, Côte d'Ivoire.* Bulletin de la Société de pathologie exotique, 2013. **106**(4): p. 272-277.

155. N'Guessan, R.D., et al., *Determinants of Rabies Post-exposure Prophylaxis Drop-Out in the Region of San-Pedro, Côte d'Ivoire.* Front Vet Sci, 2022. **9**: p. 878886.

156. Zhang, W., et al., *Analysis of Factors Influencing the Course of Rabies Vaccinations: One Year Study on Compliance of Rabies Vaccination Regimens in Haidian District of Beijing.* Patient Preference and Adherence, 2022. **Volume 16**: p. 2913-2920.

157. Guo, C., et al., *Exposure history, post-exposure prophylaxis use, and clinical characteristics of human rabies cases in China, 2006-2012.* Sci Rep, 2018. **8**(1): p. 17188.

158. Penjor, K., T. Tenzin, and R.K. Jamtsho, *Determinants of health seeking behavior of animal bite victims in rabies endemic South Bhutan: a community-based contact-tracing survey.* BMC Public Health, 2019. **19**(1): p. 237.

159. Veloso, R.D., et al., *[Abandon reasons of post-exposure human anti-rabies treatment in Porto Alegre (RS, Brazil)].* Cien Saude Colet, 2011. **16**(2): p. 537-46.

160. Tarantola, A., et al., *Rabies Postexposure Prophylaxis Noncompletion After Dog Bites: Estimating the Unseen to Meet the Needs of the Underserved.* American Journal of Epidemiology, 2018. **187**(2): p. 306-315.

161. Tran, C.H., et al., *Rabies post-exposure prophylaxis initiation and adherence among patients in Vietnam, 2014–2016.* Vaccine, 2019. **37**: p. A54-A63.

162. Yurachai, O., S. Hinjoy, and R.M. Wallace, *An epidemiological study of suspected rabies exposures and adherence to rabies post-exposure prophylaxis in Eastern Thailand, 2015.* PLOS Neglected Tropical Diseases, 2020. **14**(2): p. e0007248.

163. Castillo-Neyra, R., et al., *Behavioral and structural barriers to accessing human post-exposure prophylaxis and other preventive practices in Arequipa, Peru, during a canine rabies epidemic.* PLoS Negl Trop Dis, 2020. **14**(7): p. e0008478.

164. Madjadinan, A., et al., *Identification of risk factors for rabies exposure and access to post-exposure prophylaxis in Chad.* Acta Trop, 2020. **209**: p. 105484.

165. Beyene, T.J., et al., *Determinants of health seeking behaviour following rabies exposure in Ethiopia.* Zoonoses Public Health, 2018. **65**(4): p. 443-453.

166. Mohammad Basir, M.F., et al., *The Determinants of Non-compliance on Rabies Vaccination in North-West Peninsular Malaysia.* Journal of Epidemiology and Global Health, 2023. **13**(1): p. 1-10.

167. Diallo, M.K., et al., *Human rabies post exposure prophylaxis at the Pasteur Institute of Dakar, Senegal: trends and risk factors.* BMC Infectious Diseases, 2019. **19**(1): p. 321.

168. De Nardo, P., et al., *A retrospective evaluation of bites at risk of rabies transmission across 7 years: The need to improve surveillance and reporting systems for rabies elimination.* PLoS One, 2018. **13**(7): p. e0197996.

169. Hampson, K., et al., *Rabies exposures, post-exposure prophylaxis and deaths in a region of endemic canine rabies.* PLoS Negl Trop Dis, 2008. **2**(11): p. e339.

170. Olarinmoye, A.O., et al., *Time series analysis and mortality model of dog bite victims presented for treatment at a referral clinic for rabies exposure in Monrovia, Liberia, 2010-2013.* Spat Spatiotemporal Epidemiol, 2017. **22**: p. 1-13.

171. Whitehouse, E.R., et al., *Human rabies despite post-exposure prophylaxis: a systematic review of fatal breakthrough infections after zoonotic exposures.* The Lancet Infectious Diseases, 2023. **23**(5): p. e167-e174.

172. Dodet, B., et al., *Rabies awareness in eight Asian countries.* Vaccine, 2008. **26**(50): p. 6344-6348.

173. Esmaeilzadeh, F., et al., *Epidemiology of Animal Bites and Factors Associated With Delays in Initiating Post-exposure Prophylaxis for Rabies Prevention Among Animal Bite Cases: A Population-based Study.* Journal of Preventive Medicine and Public Health, 2017. **50**(3): p. 210-216.

174. Liu, Q., et al., *Improper wound treatment and delay of rabies post-exposure prophylaxis of animal bite victims in China: Prevalence and determinants.* PLOS Neglected Tropical Diseases, 2017. **11**(7): p. e0005663.

175. Joseph, J., et al., *Determinants of delay in initiating post-exposure prophylaxis for rabies prevention among animal bite cases: Hospital based study.* Vaccine, 2013. **32**(1): p. 74-77.

176. Larson, H.J., et al., *The State of Vaccine Confidence 2016: Global Insights Through a 67-Country Survey.* EBioMedicine, 2016. **12**: p. 295-301.

177. Reyes, M., E.C. Dee, and B.L. Ho, *Vaccination in the Philippines: experiences from history and lessons for the future.* Hum Vaccin Immunother, 2021. **17**(6): p. 1873-1876.

178. *Tiff over anti-tetanus vaccine now erupted into battle. International / Philippines.* Vaccine Wkly, 1995: p. 11-3.

179. Catindig, N., et al., *Tetanus toxoid and spontaneous abortions: is there epidemiological evidence of an association?* The Lancet, 1996. **348**(9034): p. 1098-1099.

180. Dyer, O., *Philippines measles outbreak is deadliest yet as vaccine scepticism spurs disease comeback.* BMJ, 2019: p. l739.

181. Larson, H.J., K. Hartigan-Go, and A. De Figueiredo, *Vaccine confidence plummets in the Philippines following dengue vaccine scare: why it matters to pandemic preparedness.* Human Vaccines & Immunotherapeutics, 2019. **15**(3): p. 625-627.

182. Davlin, S.L., et al., *Knowledge, attitudes, and practices regarding rabies in Filipinos following implementation of the Bohol Rabies Prevention and Elimination Programme.* Epidemiology and Infection, 2014. **142**(7): p. 1476-1485.

183. Briggs, D.J. and S.M. Moore, *Chapter 16 - Public health management of humans at risk*, in *Rabies (Fourth Edition)*, A.R. Fooks and A.C. Jackson, Editors. 2020, Academic Press: Boston. p. 527-545.

184. Lungten, L., et al., *Assessment of the rabies education among middle secondary school students of southeastern Bhutan.* PLoS One, 2022. **17**(12): p. e0276862.

185. Hasanov, E., et al., *Assessing the impact of public education on a preventable zoonotic disease: rabies.* Epidemiol Infect, 2018. **146**(2): p. 227-235.

186. Veloso, R.D., et al., *Motivos de abandono do tratamento antirrábico humano pós-exposição em Porto Alegre (RS, Brasil).* Ciência & Saúde Coletiva, 2011. **16**(2): p. 537-546.

187. Zamina, B.Y.G., et al., *[Improved adherence to post-exposure prophylaxis through the use of mobile telephony at the Treichville anti-rabies center, Côte d'Ivoire.].* Sante Publique, 2018. **30**(4): p. 545-554.

188. Etheart, M.D., et al., *Effect of counselling on health-care-seeking behaviours and rabies vaccination adherence after dog bites in Haiti, 2014–15: a retrospective follow-up survey.* The Lancet Global Health, 2017. **5**(10): p. e1017-e1025.

189. World Health Organization (WHO), W.O.f.A.H.O., *Global elimination of rabies: the time is now*. 2016.

190. ATLAS.ti Scientific Development GmbH, *ATLAS.ti*. 2020, ATLAS.ti Scientific Software Development GmbH: Berlin, Germany.

191. Braun, V. and V. Clarke, *Using thematic analysis in psychology.* Qualitative Research in Psychology, 2006. **3**(2): p. 77-101.

192. CNN Philippines. *TIMELINE: How the Philippines is handling COVID-19*. 2021 [cited 2022; Available from: https://www.cnnphilippines.com/news/2020/4/21/interactive-timeline-PH-handling-COVID-19.html.

193. SunStar. *Timeline: Covid-19 in the Philippines*. 2020 12/05/2020 [cited 2022; Available from: https://www.sunstar.com.ph/ampArticle/1856059.

194. Liu, Y., N. Di, and X. Tao, *Knowledge, practice and attitude towards HPV vaccination among college students in Beijing, China.* Hum Vaccin Immunother, 2020. **16**(1): p. 116-123.

195. Kaneko, M., et al., *Better Patient Experience is Associated with Better Vaccine Uptake in Older Adults: Multicentered Cross-sectional Study.* J Gen Intern Med, 2020. **35**(12): p. 3485-3491.

196. Vu, M., et al., *Practice-, provider- and patient-level facilitators of and barriers to HPV vaccine promotion and uptake in Georgia: a qualitative study of healthcare providers' perspectives.* Health Educ Res, 2020. **35**(6): p. 512-523.

197. Haradanhalli, R.S., D.H. AN, and S.T. Varadappa, *Cost of rabies post exposure prophylaxis in different healthcare settings in six states of India.* Indian J Public Health, 2019. **63**(Supplement): p. S44-s47.

198. Maravilla, J., et al., *Exploring indirect impacts of COVID-19 on local health systems from the perspectives of health workers and higher education stakeholders in the Philippines using a phenomenological approach.* The Lancet Regional Health - Western Pacific, 2023. **30**: p. 100585.

199. Harris, R.C., et al., *Impact of COVID-19 on routine immunisation in South-East Asia and Western Pacific: Disruptions and solutions.* The Lancet Regional Health - Western Pacific, 2021. **10**: p. 100140.

200. D'Angelo, S., et al., *Predictors and Consequences of Not Seeking Healthcare during the COVID-19 Pandemic: Findings from the HEAF Cohort.* Int J Environ Res Public Health, 2022. **19**(20).

201. Evans, B. and T. Jombart, *Worldwide routine immunisation coverage regressed during the first year of the COVID-19 pandemic.* Vaccine, 2022. **40**(26): p. 3531-3535.

202. Watson, G., et al., *'Do I, don't I?' A qualitative study addressing parental perceptions about seeking healthcare during the COVID-19 pandemic.* Arch Dis Child, 2021. **106**(11): p. 1118-1124.

203. Furnham, A., *Response bias, social desirability and dissimulation.* Personality and Individual Differences, 1986. **7**(3): p. 385-400.

204. Fisher, R.J., *Social Desirability Bias and the Validity of Indirect Questioning.* Journal of Consumer Research, 1993. **20**(2): p. 303-315.

205. Bispo Júnior, J.P., *Social desirability bias in qualitative health research.* Rev Saude Publica, 2022. **56**: p. 101.

206. Bergen, N. and R. Labonté, *"Everything Is Perfect, and We Have No Problems": Detecting and Limiting Social Desirability Bias in Qualitative Research.* Qualitative Health Research, 2020. **30**(5): p. 783-792.

207. Scott, K., O. Ummer, and A.E. LeFevre, *The devil is in the detail: reflections on the value and application of cognitive interviewing to strengthen quantitative surveys in global health.* Health Policy Plan, 2021. **36**(6): p. 982-995.

208. Microsoft, *Excel*. 2019: Redmond, WA.

209. StataCorp., *Stata Statistical Software: Release 16*. 2019, StataCorp LLC.: College Station, TX.

210. Hampson, K., et al., *Modelling to inform prophylaxis regimens to prevent human rabies.* Vaccine, 2019. **37**: p. A166-A173.

211. Hampson, K., et al., *The potential effect of improved provision of rabies post-exposure prophylaxis in Gavi-eligible countries: a modelling study.* The Lancet Infectious Diseases, 2019. **19**(1): p. 102-111.

212. Hampson, K., S. Cleaveland, and D. Briggs, *Evaluation of Cost-Effective Strategies for Rabies Post-Exposure Vaccination in Low-Income Countries.* PLoS Neglected Tropical Diseases, 2011. **5**(3): p. e982.

213. Rysava, K., et al., *On the path to rabies elimination: The need for risk assessments to improve administration of post-exposure prophylaxis.* Vaccine, 2019. **37**: p. A64-A72.

214. Kisaka, S., et al., *"As long as the patient tells you it was a dog that bit him, why do you need to know more?" A qualitative study of how healthcare workers apply clinical guidelines to treat dog bite injuries in selected hospitals in Uganda.* PLOS ONE, 2021. **16**(7): p. e0254650.

215. Medina, D.J.O., et al., *World Rabies Day campaign in the Philippines.* Tropical Diseases, Travel Medicine and Vaccines, 2016. **2**(1).

216. Office of the President of the Philippines, *Community Quarantine Over the Entire Luzon and Further Guidelines for the Managament of the Coronavirus Disease 2019 (COVID-19) Situation*. 2020: Official Gazette.

217. Santos, A.P., *Coronavirus: Philippines quarantines island of 57 million people*, in *Al Jazeera*. 2020.

218. *Duterte places Metro Manila under GCQ beginning June 1*, in *GMA News Online*. 2020: https://www.gmanetwork.com/news/topstories/nation/740232/duterte-places-metro-manila-under-gcq-despite-warnings-from-experts/story/.

219. CNN Philippines Staff, *Metro Manila eases to GCQ on June 1*, in *CNN Philippines*. 2020.

220. CNN Philippines Staff, *Metro Manila, four provinces shift to stricter ECQ for one week*, in *CNN Philippines*. 2021.

221. Medenilla, S.P., *NCR, 12 regions still under GCQ in February*, in *Business Mirror*. 2021.

222. Fonbuena, C., *Manila lockdown diary: 'I went into labour but had to walk to the clinic to give birth'*, in *The Guardian*. 2020.

223. Nadal, D., et al., *Rabies and the pandemic: lessons for One Health.* Trans R Soc Trop Med Hyg, 2022. **116**(3): p. 197-200.

224. Gongal, G., et al., *The impact of COVID-19 pandemic on rabies post-exposure prophylaxis services in Asia.* Human Vaccines & Immunotherapeutics, 2022. **18**(5): p. 1-4.

225. Raynor, B., et al., *The impact of the COVID-19 pandemic on rabies reemergence in Latin America: The case of Arequipa, Peru.* PLoS Negl Trop Dis, 2021. **15**(5): p. e0009414.

226. Rasizadeh, R. and B. Hossein Bannazadeh, *Increase in rabies cases during COVID-19 pandemic: Is there a connection?* The Journal of Infection in Developing Countries, 2023. **17**(03): p. 335-336.

227. Fetters, M.D., L.A. Curry, and J.W. Creswell, *Achieving integration in mixed methods designs-principles and practices.* Health Serv Res, 2013. **48**(6 Pt 2): p. 2134-56.

228. Krishnamoorthy, Y., et al., *Factors related to vaccine hesitancy during the implementation of Measles-Rubella campaign 2017 in rural Puducherry-A mixed-method study.* J Family Med Prim Care, 2019. **8**(12): p. 3962-3970.

229. Patel, H., et al., *Barriers and motivators for uptake of cervical cancer prevention strategies in Eastern Europe: the perspective from Latvia.* Acta Dermatovenerol Alp Pannonica Adriat, 2019. **28**(3): p. 107-111.

230. Kesten, J.M., et al., *Mixed-methods study in England and Northern Ireland to understand young men who have sex with men's knowledge and attitudes towards human papillomavirus vaccination.* BMJ Open, 2019. **9**(5): p. e025070.

231. O'Grady, K.A., et al., *Uptake of influenza vaccination in pregnancy amongst Australian Aboriginal and Torres Strait Islander women: a mixed-methods pilot study.* BMC Res Notes, 2015. **8**: p. 169.

232. Chuang, E., et al., *Primary care team- and clinic level factors affecting HPV vaccine uptake.* Vaccine, 2017. **35**(35, Part B): p. 4540-4547.

233. Guzman, F.D., et al., *Clinical, epidemiological, and spatial features of human rabies cases in Metro Manila, the Philippines from 2006 to 2015.* PLoS Negl Trop Dis, 2022. **16**(7): p. e0010595.

234. Dimaano, E.M., et al., *Clinical and epidemiological features of human rabies cases in the Philippines: a review from 1987 to 2006.* International Journal of Infectious Diseases, 2011. **15**(7): p. e495-e499.

235. Tran, C.H., et al., *Rabies vaccine initiation and adherence among animal-bite patients in Haiti, 2015.* PLOS Neglected Tropical Diseases, 2018. **12**(11): p. e0006955.

236. Tenzin, N.K. Dhand, and M.P. Ward, *Human rabies post exposure prophylaxis in Bhutan, 2005–2008: Trends and risk factors.* Vaccine, 2011. **29**(24): p. 4094-4101.

237. Gallup, *Wellcome Global Monitor 2018 - First Wave Findings*. 2019.

238. Harris, P.A., et al., *The REDCap consortium: Building an international community of software platform partners.* Journal of Biomedical Informatics, 2019. **95**: p. 103208.

239. Harris, P.A., et al., *The REDCap Mobile Application: a data collection platform for research in regions or situations with internet scarcity.* JAMIA Open, 2021. **4**(3).

240. Harris, P.A., et al., *Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support.* Journal of Biomedical Informatics, 2009. **42**(2): p. 377-381.

241. Quiambao, B.P., et al., *Rabies post-exposure prophylaxis with purified equine rabies immunoglobulin: One-year follow-up of patients with laboratory-confirmed category III rabies exposure in the Philippines.* Vaccine, 2009. **27**(51): p. 7162-7166.

242. McCambridge, J., J. Witton, and D.R. Elbourne, *Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects.* J Clin Epidemiol, 2014. **67**(3): p. 267-77.

243. Government Service Insurance System (GSIS). *Lowering the Retirement Age of Government Employees*. 2023 [cited 2023 August 24]; Available from: https://www.gsis.gov.ph/frequently-asked-questions/lowering-the-retirement-age-of-government-employees/.

244. Reñosa, M.D.C., et al., *Misinformation, infighting, backlash, and an 'endless' recovery; policymakers recount challenges and mitigating measures after a vaccine scare in the Philippines.* Glob Health Action, 2022. **15**(1): p. 2077536.

245. De Figueiredo, A., et al., *Mapping global trends in vaccine confidence and investigating barriers to vaccine uptake: a large-scale retrospective temporal modelling study.* The Lancet, 2020. **396**(10255): p. 898-908.

246. Brackstone, K., et al., *COVID-19 vaccine hesitancy and confidence in the Philippines and Malaysia: A cross-sectional study of sociodemographic factors and digital health literacy.* PLOS Glob Public Health, 2022. **2**(10): p. e0000742.

247. Larson, H.J., et al., *Measuring trust in vaccination: A systematic review.* Hum Vaccin Immunother, 2018. **14**(7): p. 1599-1609.

248. Oldenburg, C.E., et al., *Adherence to Post-Exposure Prophylaxis for Non-forcible Sexual Exposure to HIV: A Systematic Review and Meta-Analysis.* AIDS and Behavior, 2014. **18**(2): p. 217-225.

249. Jefferds, M.D., et al., *Adherence to antimicrobial inhalational anthrax prophylaxis among postal workers, Washington, D.C., 2001.* Emerg Infect Dis, 2002. **8**(10): p. 1138-44.

250. Shepard, C.W., et al., *Antimicrobial postexposure prophylaxis for anthrax: adverse events and adherence.* Emerg Infect Dis, 2002. **8**(10): p. 1124-32.

251. Saunders, B., et al., *Saturation in qualitative research: exploring its conceptualization and operationalization.* Quality & Quantity, 2018. **52**(4): p. 1893-1907.

252. Squires, A., *Methodological challenges in cross-language qualitative research: a research review.* Int J Nurs Stud, 2009. **46**(2): p. 277-87.

253. Temple, B. and R. Edwards, *Interpreters/Translators and Cross-Language Research: Reflexivity and Border Crossings.* International Journal of Qualitative Methods, 2002. **1**(2): p. 1-12.

254. Duru, J.I., et al., *Contributions of Volunteer Community Mobilizers to Polio Eradication in Nigeria: The Experiences of Non-governmental and Civil Society Organizations.* Am J Trop Med Hyg, 2019. **101**(4_Suppl): p. 74-84.

255. Schoeppe, J., et al., *The Immunity Community: A Community Engagement Strategy for Reducing Vaccine Hesitancy.* Health Promot Pract, 2017. **18**(5): p. 654-661.

256. Sachs, J.D., et al., *The Lancet Commission on lessons for the future from the COVID-19 pandemic.* Lancet, 2022. **400**(10359): p. 1224-1280.

257. Jarrett, C., et al., *Strategies for addressing vaccine hesitancy - A systematic review.* Vaccine, 2015. **33**(34): p. 4180-90.

258. Jacobson Vann, J.C., et al., *Patient reminder and recall interventions to improve immunization rates.* Cochrane Database Syst Rev, 2018. **1**(1): p. Cd003941.

259. Parker, C., S. Scott, and A. Geddes, *Snowball Sampling*. 2019: London.

260. Science and Technology Research Partnership for Sustainable Development Program, *SATREPS 2022*. 2022. p. 61.

261. Gouda, H.N., et al., *New challenges for verbal autopsy: Considering the ethical and social implications of verbal autopsy methods in routine health information systems.* Social Science & Medicine, 2017. **184**: p. 65-74.

262. Aborigo, R.A., et al., *Cultural imperatives and the ethics of verbal autopsies in rural Ghana.* Global Health Action, 2013. **6**(1): p. 18570.

263. Hinga, A., et al., *The ethical implications of verbal autopsy: responding to emotional and moral distress.* BMC Medical Ethics, 2021. **22**(1).

264. Gouda, H.N., et al., *"Whenever they cry, I cry with them": Reciprocal relationships and the role of ethics in a verbal autopsy study in Papua New Guinea.* Soc Sci Med, 2016. **163**: p. 1-9.

265. Chandramohan, D., et al., *Editorial: Ethical issues in the application of verbal autopsies in mortality surveillance systems.* Tropical Medicine and International Health, 2005. **10**(11): p. 1087-1089.

266. Treviño-Siller, S., et al., *How to deal with the suffering: Utility of an emotional containment strategy to collect data for verbal autopsies in Mexico.* Death Studies, 2022. **46**(4): p. 1015-1020.

267. Lushasi, K., et al., *One Health in Practice: Using Integrated Bite Case Management to Increase Detection of Rabid Animals in Tanzania.* Front Public Health, 2020. **8**: p. 13.

268. Philippines Statistics Authority. *Functional literacy rate of Filipinos by exposure to different forms of mass media ranges from 92.6 percent to 97.1 percent in 2019*. 2020 [cited 2023 December 9]; Available from: https://psa.gov.ph/statistics/education-mass-media.

269. Tong, A., P. Sainsbury, and J. Craig, *Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups.* International Journal for Quality in Health Care, 2007. **19**(6): p. 349-357.

270. Kessels, J., et al., *Rabies post-exposure prophylaxis: A systematic review on abridged vaccination schedules and the effect of changing administration routes during a single course.* Vaccine, 2019. **37**: p. A107-A117.

271. Yu, P., et al., *Production and evaluation of a chromatographically purified Vero cell rabies vaccine (PVRV) in China using microcarrier technology.* Hum Vaccin Immunother, 2012. **8**(9): p. 1230-5.

272. Sampath, G., et al., *Immunogenicity and safety study of Indirab: A Vero cell based chromatographically purified human rabies vaccine.* Vaccine, 2010. **28**(24): p. 4086-4090.

10 Appendix

10.1 Literature Review Search Strategy

Search: **rabies AND (vaccin* OR post-exposure prophylaxis) AND (uptake OR adherence OR initiation OR compliance OR completion)** Filters: **Humans**
(("rabies"[MeSH Terms] OR "rabies"[All Fields]) AND ("vaccin*"[All Fields] OR ("post exposure prophylaxis"[MeSH Terms] OR ("post exposure"[All Fields] AND "prophylaxis"[All Fields]) OR "post exposure prophylaxis"[All Fields] OR ("post"[All Fields] AND "exposure"[All Fields] AND "prophylaxis"[All Fields]) OR "post exposure prophylaxis"[All Fields])) AND ("uptake"[All Fields] OR "uptakes"[All Fields] OR "uptaking"[All Fields] OR ("adherance"[All Fields] OR "adhere"[All Fields] OR "adhered"[All Fields] OR "adherence"[All Fields] OR "adherences"[All Fields] OR "adherent"[All Fields] OR "adherents"[All Fields] OR "adherer"[All Fields] OR "adherers"[All Fields] OR "adheres"[All Fields] OR "adhering"[All Fields]) OR ("initial"[All Fields] OR "initially"[All Fields] OR "initials"[All Fields] OR "initiate"[All Fields] OR "initiated"[All Fields] OR "initiates"[All Fields] OR "initiating"[All Fields] OR "initiation"[All Fields] OR "initiations"[All Fields] OR "initiator"[All Fields] OR "initiators"[All Fields]) OR ("compliances"[All Fields] OR "patient compliance"[MeSH Terms] OR ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields] OR "compliance"[All Fields] OR "compliance"[MeSH Terms]) OR ("complete"[All Fields] OR "completed"[All Fields] OR "completely"[All Fields] OR "completeness"[All Fields] OR "completer"[All Fields] OR "completers"[All Fields] OR "completes"[All Fields] OR "completing"[All Fields] OR "completion"[All Fields] OR "completions"[All Fields]))) AND (humans[Filter])
Translations
rabies: "rabies"[MeSH Terms] OR "rabies"[All Fields]
post-exposure prophylaxis: "post-exposure prophylaxis"[MeSH Terms] OR ("post-exposure"[All Fields] AND "prophylaxis"[All Fields]) OR "post-exposure prophylaxis"[All Fields] OR ("post"[All Fields] AND "exposure"[All Fields] AND "prophylaxis"[All Fields]) OR "post exposure prophylaxis"[All Fields]
vaccin*: "vaccin"[Supplementary Concept] OR "vaccin"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "vaccinable"[All Fields] OR "vaccinal"[All Fields] OR "vaccinate"[All Fields] OR "vaccinated"[All Fields] OR "vaccinates"[All Fields] OR "vaccinating"[All Fields] OR "vaccinations"[All Fields] OR "vaccination's"[All Fields] OR "vaccinator"[All Fields] OR "vaccinators"[All Fields] OR "vaccine's"[All Fields] OR "vaccined"[All Fields] OR "vaccines"[Supplementary Concept] OR "vaccines"[All Fields] OR "vaccine"[All Fields] OR "vaccines"[MeSH Terms] OR "vaccins"[All Fields]
uptake: "uptake"[All Fields] OR "uptakes"[All Fields] OR "uptaking"[All Fields]
adherence: "adherance"[All Fields] OR "adhere"[All Fields] OR "adhered"[All Fields] OR "adherence"[All Fields] OR "adherences"[All Fields] OR "adherent"[All Fields] OR

"adherents"[All Fields] OR "adherer"[All Fields] OR "adherers"[All Fields] OR "adheres"[All Fields] OR "adhering"[All Fields]
initiation: "initial"[All Fields] OR "initially"[All Fields] OR "initials"[All Fields] OR "initiate"[All Fields] OR "initiated"[All Fields] OR "initiates"[All Fields] OR "initiating"[All Fields] OR "initiation"[All Fields] OR "initiations"[All Fields] OR "initiator"[All Fields] OR "initiators"[All Fields]
compliance: "compliances"[All Fields] OR "patient compliance"[MeSH Terms] OR ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields] OR "compliance"[All Fields] OR "compliance"[MeSH Terms]
completion: "complete"[All Fields] OR "completed"[All Fields] OR "completely"[All Fields] OR "completeness"[All Fields] OR "completer"[All Fields] OR "completers"[All Fields] OR "completes"[All Fields] OR "completing"[All Fields] OR "completion"[All Fields] OR "completions"[All Fields]

10.2 Data Collection Instruments

10.2.1 Study 1: Provider Interview Guide

[Interview to be carried out by OO at the ABTC and recorded. If participants decline recorded interviews, notes will be made instead. Interviews will be conducted with doctors, pharmacists, nurses, registry staff, administrative staff, and any other staff along the patient pathway at the ABTC. The interviews will be used descriptively to provide context and an understanding of patient and provider experiences.]

This interview will include questions about your responsibilities, ABTC logistics, and patient interactions, it is aimed at understanding provider and patient experiences at the ABTC and to provide context for the rabies vaccine landscape at SLH.

Staff roles & experiences

1. What is your role and responsibility at the ABTC?
2. How many patients do you see per day?
3. How long have you worked at the SLH ABTC[1]?
4. How has the COVID-19 pandemic changed the ABTC?
    Probes: Has there been change in guidance including social disatancing or limiting the number of patients? Has there been a change to the number of patients? Do patients express a fear of being in the hospital?

Patient flow & assessments

5. How many days after a bite do patients usually present to the ABTC?
6. How do you carry out wound evaluation and decide if a patient requires vaccination?
    Probes: Do you have a set of guidelines? Did you receive training or learn wound evaluation in an initial rotation? How do you decide if they require IM/ID?
7. How long do you think each patient spends at the ABTC? (minutes/hours)
    Probes: What are the steps they go through from registration to exit?

Vaccine attitudes & refusal

8. What information do you give to patients about vaccines?
    Probes: Do you give information about the schedule? Do you discuss the importance of completing the vaccination schedule? What is the vaccine schedule?
9. Do patients decline to receive the vaccine after you have recommended it?
    Probes: How often do patients decline vaccines? (1 in 5,10,20? 1 a day? 1 a week?)
10. What happens when a patient declines a vaccine?
    Probe: Do they state reasons for declining vaccines? Do you provide any further information? Do you discuss options or encourage them to reconsider vaccination or address any concerns? Is the decline noted on their patient record? Is a waiver signed and how does it go on their record?
11. Do category 1 patients, who do not require vaccines, request, and pay for vaccines?
    Probes: How often do these patients request vaccination? (1 in 5,10,20? 1 a day? 1 a week?)

12. Do you recommend any deviations from the vaccine guidelines?
    Probes: Why? How is the decision reached?

Vaccine adherence & follow up visits

13. During follow up dose visits, have patients expressed concerns about the vaccine causing adverse effects?
    Probes: How often do patients express concerns about discomfort, symptoms, or adverse effects following vaccination? (1 in 5,10,20? 1 a day? 1 a week?)
14. What other issues do they mention? What are their barriers to receiving follow up vaccines?
15. How often are patients late for their scheduled vaccines?
    Probes: How many days behind schedule are they? Do they give reasons for the delay? If so, what reasons do they give?
    What is the procedure for late vaccines? Do you restart? How many days is the cutoff for restart?
16. Do you know if patients receive follow up doses at other ABTCs?
    Probes: Perhaps they receive the second dose elsewhere and return to SLH for third dose?

Vaccine

17. What do patients pay for at the ABTC? (needles, RIG, tetanus vaccine, antibiotics)
    Probes: How often do they pay for vaccines? How much do they pay? Do patients discuss cost as a hindrance to receiving the vaccine?
18. Are there different brand of vaccines?
    Probes: Which is most common?
19. Are there times when there are vaccines stockouts and patients cannot receive vaccines?
    Probes: How often are there stockouts? (Once a week/month?) Do you direct patients to other ABTCs or private pharmacies? How much do rabies vaccines at private pharmacies cost?

Medical Records

20. If the patients forget to give the blotter sheet/ registry data slip back, how is that entered into the system? What happens if they come back for their second/third doses?
21. Do patients come to SLH for their follow up doses? How is the data recorded for their previous doses?
22. Is the NaRIS system used or only iHOMIS?

Thank you for your participation. If you would you be interested in receiving findings from the study, please leave your email address with Mean/Siena.

10.2.2 Study 2: Retrospective Data Variables

These data variables were extracted from the San Lazaro Hospital Epidemiology Department's database of rabies vaccines dispensed at the Animal Bite Treatment Centre.

	Variable	Description	Notes
1.	hospitalid	Hospital ID	
2.	birthdate	DOB	
3.	patage	Age in years	Gives ages in years, months and days. E.g. patage 35 years, patagemo 11 months, patagedy 30 days
4.	patagemo	Age in months	
5.	patagedy	Age in days	
6.	patagehr	Age in hours	Mostly missing
7.	patsex	Sex	
8.	treatmentdescription	Dog or cat bite & dose number	e.g. DOG= dog bite 1st dose. CAT2= cat bite 2nd dose
9.	opdconsultationdate	Joint date & time variable	
10.	opdconsultationtime	Joint date & time variable	~15% missing. Used opdconsultationdate
11.	treatmentcode	Dog or cat bite & dose number	
12.	opdrem	Vaccine type	223 unique values. "pvrv" or "pcec" = 195,642 values
13.	city	City	Patient address
14.	region	Region	
15.	province	Province	
16.	patstr	Patient street	
17.	provincename	Note variable	Patient notes including other symptoms. 38 records
18.	opddisp		blank
19.	diagtext		blank
20.	opdbitecat	Exposure categories	Only 5,463 values

10.2.3 Study 3: Patient Survey

Day 0

Patient screening

Record ID	_____
Date of screening	_____
Age	_____
Gender	◯ Female ◯ Male
Type of patient approached	◯ New patient for first time vaccination ◯ Follow-up patient for vaccination
Is the patient potential participant?	◯ Yes ◯ No
If No, what is the reason?	◯ Category 1 ◯ Minor w/out consenting adult ◯ Previous vaccination was done outside SLH
If Yes, Did the patient participate?	◯ Yes ◯ No
If No, what was the reason for refusal?	_____

Demographics

Date of Interview	_____
Study ID	_____
Hospital ID number	_____
Name of Respondent	_____ (Surname, First name, Middle name)
Phone Number	_____ (09*********)
Please provide alternative phone number, in case the participant's number cannot be reached.	
Phone Number	_____
Are you the patient today?	◯ Yes ◯ No
Relationship to the patient?	◯ Parent ◯ Grandparent ◯ Nanny ◯ Sibling ◯ Other guardian
Date of birth	_____
Age	_____
Gender	◯ Male ◯ Female ◯ Prefer not to answer

City of Residence	◯ Manila City ◯ Quezon City ◯ Caloocan City ◯ Las Pinas City ◯ Makati City ◯ Malabon City ◯ Mandaluyong City ◯ Marikina City ◯ Muntinlupa City ◯ Navotas City ◯ Paranaque City ◯ Pasay City ◯ Pasig City ◯ Pateros ◯ Quezon City ◯ San Juan City ◯ Taguig City ◯ Valenzuela City ◯ Unknown ◯ Outside Metro Manila
Barangay	_____
How long does it take you to get to SLH?	_____ (from your place to SLH)
Highest educational status	◯ None ◯ Primary ◯ Secondary ◯ Vocational ◯ Tertiary ◯ Post Graduate ◯ Prefer not to answer
Estimated monthly income	◯ < ₱ 5,000 ◯ ₱ 5,000 - ₱ 10,000 ◯ ₱ 10,000 - ₱ 15,000 ◯ ₱ 15,000 - ₱ 20,000 ◯ > ₱ 20,000
Homeowner	◯ Yes ◯ No
If not, How much do you pay for rent?	_____

Rabies Risk and Bite Characteristics

What brought you to the ABTC?	◯ Rabies Vaccine ◯ Wound care ◯ Tetanus Vaccine ◯ Other
Other:	_____
Do you own pets?	◯ Yes ◯ No
What type of pet?	☐ Dog ☐ Cat ☐ Other Mammal ☐ Other Animal
If dog, is it vaccinated?	◯ Yes ◯ No
When did it receive its last vaccination	_____
Do you know if anyone in your community was bitten by a dog and did not seek medical care, go to an ABTC, or get a rabies vaccine?	◯ Yes ◯ No
Were they bitten by the same dog?	◯ Yes ◯ No
Could you call or send a message asking if they are willing to participate in the study?	◯ Yes ◯ No
Referral name	_____
Referral Contact Number	_____

A rabies exposure is a bite or scratch, or eating mammals like dogs, cats or rodents that may have rabies.

What type of exposure did you have?	☐ Scratch ☐ Bite ☐ Multiple Bites ☐ Consumption
Where is the exposure site?	☐ Head ☐ Arms ☐ Fingers ☐ Torso ☐ Upper legs ☐ Lower legs

When did the exposure occur?	----------
Is the animal involved a pet or stray?	◯ Participant's Pet ◯ Other's Pet ◯ Stray
If pet, do you know the vaccination status of the pet?	◯ Vaccinated (within the last 1 year) ◯ Unvaccinated ◯ Vaccination status unknown
Is the animal alive?	◯ Yes ◯ No ◯ Unknown
When did the animal die?	----------
What treatment did you carry out before ABTC?	☐ Wound washing only ☐ Medical consultation ☐ None
Category of Exposure	◯ Category I ◯ Category II ◯ Category III
Did you receive rabies immunoglobulin?	◯ Yes ◯ No
Have you had a rabies vaccine prior to this rabies exposure?	◯ Yes ◯ No
If yes, Was it before or after a rabies exposure?	◯ Preexposure ◯ Postexposure
When was the vaccine received?	----------
How many doses were received?	◯ 1 ◯ 2 ◯ 3 ◯ 4+

Barriers and Facilitators

Did you pay for your vaccine?	◯ Yes ◯ No
How much money did you spend today at the ABTC?	_____ (e.g. the cost of syringes and transport including meals)
Transportation	_____
Food	_____
Syringe	_____
Registration Card	_____
How much time did you spend at the ABTC?	_____ (can ask what time they arrived and calculate)
How many doses were you recommended and what days do you have to return?	◯ Full awareness of numbers of doses and days ◯ Aware of number of doses ◯ Not aware of follow-up doses (Participant should state 3 follow-up doses on days 3, 7, and 28 for full awareness. Also full awareness if participant states only first 2 doses if dog is alive. If they are unaware or partially aware, researcher should explain dose schedule.)
How did the vaccination process go? How did you feel after?	◯ Indicates poor experience or side effects ◯ No poor experience

Perceived Severity

	Death	Very serious	Not very serious	Not serious at all	Don't know
How serious would it be for someone to get rabies?	◯	◯	◯	◯	◯

Perceived Susceptibility

Do you know someone who had rabies?	◯ Yes ◯ No

How likely do you think it would be for someone to get rabies after an animal bite or scratch?

	Very likely	Likely	Not likely	Impossible	Don't know
Dog Bite	○	○	○	○	○
Dog Scratch	○	○	○	○	○
Bat Contact	○	○	○	○	○

Perceived Benefits

How much do you agree or disagree with this statement

	Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree
"Vaccines are important for children to have"?	○	○	○	○	○

Confidence

For each of these vaccines, How much do you agree that vaccines are effective?

	Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree
Rabies vaccine	○	○	○	○	○
Measles vaccine	○	○	○	○	○
Tetanus vaccine	○	○	○	○	○
Dengue vaccine	○	○	○	○	○
Covid-19 vaccine	○	○	○	○	○

Confidence

For each of these vaccines, how much do you agree that vaccines are safe?

	Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree
Rabies vaccine	○	○	○	○	○
Measles vaccine	○	○	○	○	○
Tetanus vaccine	○	○	○	○	○
Dengue vaccine	○	○	○	○	○
Covid-19 vaccine	○	○	○	○	○

Would you agree to receive for yourself covid-19 vaccine?
○ Yes
○ No

Would you agree for your child to receive Covid-19 vaccine?
○ Yes
○ No

How much do you trust each of the following?	A lot	Some	Not much	Not at all	Don't know
Doctors	○	○	○	○	○
Scientists	○	○	○	○	○
Department of Health	○	○	○	○	○
News media (TV, radio, newspapers)	○	○	○	○	○
Internet and Social Media	○	○	○	○	○

Rabies Exposure Contact

Do you know if anyone in your community was bitten by a dog and did not seek medical care, go to an ABTC or get rabies vaccine?	◯ Yes ◯ No (We would like to ask them questions about their dog bite experience and encourage them to receive a rabies vaccine)
If, Yes Were they bitten by the same dog?	◯ Yes ◯ No
Could you call or send a message asking if they are willing to participate in the study?	◯ Yes ◯ No (If Yes, Please provide their name and contact number. They can also contact us to participate)
Name of referral	_____
Contact number of referral	_____ (+639)
Nurses Notes	_____

Day 30

Study 3 Day 30 Followup

Record ID	_____
Date & time of survey	_____

We're calling you because you enrolled in the rabies vaccine study during your recent visit to the SLH ABTC. We mentioned we would be calling a month after your first visit. We would like to ask you some questions.

Study ID	_____
1. Did you complete your original schedule of rabies vaccine?	◯ Yes ◯ No (Could be 4 or 5 - ID or IM)
2. How many rabies vaccine doses did you receive?	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
If incomplete, Were you aware you had to receive 4/5 doses?	◯ Yes ◯ No
What were the reasons you were unable to receive the 4/5 doses?	☐ Forgot ☐ No time/work constraints ☐ No money ☐ Did not think the doses were necessary ☐ Dog that bit/scratched participant was alive after day 14 ☐ Bad experience or reaction with first dose ☐ Bad experience at the ABTC ☐ Covid Isolation ☐ Other ☐ Travel. Didn't know where to find ABTC
Please specify other reason	_____
3. Did you receive rabies immunoglobulin RIg?	◯ Yes ◯ No
Which visit did you receive the RIg?	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
4. Did you experience any symptoms after receiving the rabies vaccine?	◯ Yes ◯ No

If Yes, please specify symptoms	_____
5. Where did you receive your rabies vaccine doses ?	☐ SLH ☐ Other (Regarding doses 2, 3, 4, 5. Can choose SLH & other if doses2-5 were mixed)
Other institution or healthcare facility where you received your rabies vaccine	_____
6. Did you receive your vaccine on the scheduled days?	◯ Yes ◯ No (Have the patient say what the scheduled days are)
If not, what were the reasons for the delay?	☐ Forgot ☐ No time/work constraints ☐ No money ☐ Did not think the doses were necessary ☐ Bad experience or reaction with first dose ☐ Bad experience at the ABTC ☐ Covid isolation ☐ Travel to province ☐ Other
Please specify other reasons for delay	_____
How delayed was the dose?	_____ (Number in days)
Did the doctors restart your dose?	◯ Yes ◯ No (Only if more than 2 days)
Are you willing to restart?	◯ Yes ◯ No (Only if more than 2 days)
7. Do you know if anyone in your community was bitten by a dog and did not seek medical care, go to an ABTC, or get a rabies vaccine?	◯ Yes ◯ No (We would like to ask them questions about their dog bite experience and encourage them to receive a rabies vaccine.)
If yes, were they bitten by the same dog?	◯ Yes ◯ No
Could you call or send a message asking if they are willing to participate in the study?	◯ Yes ◯ No (If contact agrees, please provide name and number. They can also contact us to participate)
Name of referral	_____

Phone number of contact	_____
8. Have you received covid-19 vaccine?	◯ Yes ◯ No ◯ Medically Exempt
How many doses of covid-19 vaccine have you received?	◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4

10.2.4 Study 3: 30-Day Patient Interview Guide

[Interview to be carried out in person (or over the phone if in person is not feasible) 30+ days after first dose was received. It will follow the Day 30 survey where dose completion and reasons are asked. This interview will be recorded and is to elicit the factors that facilitated or prevented vaccine adherence.]

English

Participant ID no. *(prefilled)*
Name *(prefilled)*
Phone number *(prefilled)*

We will be asking some questions to hear about your experience at the ABTC and receiving your rabies vaccine doses.

1. Do you remember your bite? Where was the bite on you body? Was it a cat or a dog? What do you remember about the way the animal was behaving? Did you know the owner of the animal?
   Did the animal seem rabid? (Acting strangely, aggressively)

2. How did you decide to go to SLH for your vaccine?
   - Did you already know that people go there? Is that what people in your community do when they get bitten?
   - Were you unsure of whether to go or not? What convinced you if you were unsure?
   - Did you receive any information from your friends, family, neighbours, community?
   - What information did you receive?
   - Did anyone encourage or discourage you to seek vaccination? Did anyone say "oh you don't need rabies vaccine for that, its so small, the dog is fine"?

3. Tell me about your experience during your first rabies vaccine visit at SLH?
   Did you have a good experience? How long did you spend?
   If yes, was it easy? Fast? Convenient?
   If no, what was the problem? Was it too long? Expensive? Disorganized? Confusing? Hot? Crowded?

4. Do you feel you have enough information about the rabies and rabies vaccine?
   - Where did you receive your information from? Did you get any information from the doctors/nurses/staff at SLH (not from our staff)?
   - What do you know about rabies and rabies vaccine?
   - Is there any information you would have liked to have?

5. Would you encourage a friend or neighbour bit by a dog to seek vaccination? How about a cat? Why?
   Would you encourage them to go to SLH? Why or why not?

6. *[Show Patient rabies information leaflet available at SLH].* Have you seen this leaflet before? What do you think about it? Does it give you any new information? Is there anything missing on this leaflet that would be helpful?

State number of doses received and let the participant confirm it

7. If received >1 dose
   If vaccine received elsewhere not SLH, where did you go and why?

If the participant has received all vaccine doses

8. What were the reasons you returned to complete vaccination?
   Probes: Is it because you knew how serious rabies was? Is it because you listen to doctor's instructions? Was it easy for you to get to an ABTC?

If the participant did NOT receive all vaccine doses

9. What were the factors that prevented you from returning to SLH to complete vaccination?
   (Based on answer in survey) – please can you explain more of the reason why you couldn't complete the vaccination?
   If participant displayed high knowledge of rabies e.g. death or serious illness: you mentioned you know about rabies disease and what happens to people who get it, when you didn't complete your vaccines, were you scared?

10. What would have helped you or encouraged you to return for your doses?
    Probe: Staff, information, vaccine administration experience, reminder

11. What do you think about the clinic sending reminders about the rabies vaccine?
    Probe: Would you be happy to receive a text message or call with reminder? Which would you prefer? Would that have been helpful? Preference for type of message?

12. (*Explain rabies can lead to death, the importance of finishing vaccines. If phone interview, if they come to SLH they can receive 100 PHP transport assistance).* Now that you know rabies can lead to death, would you be able to come to SLH or go to another ABTC to complete?

Tagalog

Participant ID no. *(prefilled)*
Name *(prefilled)*
Phone number *(prefilled)*

Tatanungin ka namin ng ilang mga tanong para marinig ang tungkol sa karanasan mo sa ABTC at sa pagtanggap mo ng mga dosis ng bakuna sa rabies

1. Naaalala mo ba ang iyong kagat? Ito ba ay isang pusa o isang aso? Ang hayop ba ay tila masugid? (Kumilos nang kakaiba, agresibo,)

2. Paano ka nagpasya na pumunta sa SLH para sa iyong bakuna?
   - Alam mo na ba na ang mga tao ay pumupunta doon? Iyan ba ang ginagawa ng mga tao sa iyong komunidad kapag sila ay nakagat?
   - Nag-aalinlangan ka ba kung pupunta o hindi? Ano ang nakakumbinsi sa iyo kung hindi ka sigurado?
   - Nakatanggap ka ba ng anumang impormasyon mula sa iyong mga kaibigan, pamilya, kapitbahay, komunidad?
   - Anong impormasyon ang iyong natanggap?
   - Mayroon bang naghihikayat o humimok sa iyo na magpabakuna? May nagsabi ba na "hindi mo kailangan ng bakuna sa rabies para diyan, napakaliit nito, ayos lang ang aso"?
3. Ikuwento mo sa amin ang iyong karanasan sa una mong pagbisita sa SLH upang magpabakuna para sa rabies?
   Probes: Iyon ba ay madali lang? Mabilis? Kumbinyente?
   Masyado bang mahaba? Mahal? Hindi organisado? Nakakalito? Mainit? Siksikan?

4. Sa palagay mo ba ay mayroon kang sapat na impormasyon tungkol sa bakuna sa rabies?
   Saan mo natanggap ang iyong impormasyon? May impormasyon ba na nais mong malaman?

5. Hihikayatin mo ba ang isang kaibigan o kapitbahay na nakagat ng aso na magpabakuna?

6. *[Show Patient rabies information leaflet available at SLH].* Nakita mo na ba ang pulyetong ito noon? Ano ang tingin mo dito? Nagbibigay ba ito sa iyo ng bagong impormasyon? May kulang ba sa pulyetong ito na makakatulong sana?

State number of doses received and let the participant confirm it

7. If received >1 dose/ Kung natanggap >1 dosis
   Kung natanggap ang bakuna sa ibang lugar hindi SLH, saan ka nagpunta at bakit?

If the participant has received all vaccine doses/ Kung natanggap ng kalahok ang lahat ng dosis ng bakuna

8. Ano ang mga dahilan kaya ka bumalik sa SLH para kumpletuhin ang pagpapabakuna?

Probes: Dahil ba alam mo kung gaano kalubha ang rabies? Dahil ba nakikinig ka sa mga tagubilin ng doktor? Naging madali ba para sa iyo na makarating sa isang ABTC?

If the participant did NOT receive all vaccine doses/ Kung HINDI natanggap ng kalahok ang lahat ng dosis ng bakuna

9. Ano ang mga salik na pumigil sa iyo na bumalik sa SLH para kumpletuhin ang pagpapabakuna?
   Maaari mo bang ipaliwanag ang higit pa sa dahilan kung bakit hindi mo makumpleto ang pagbabakuna?
   If participant displayed high knowledge of rabies e.g. death or serious illness:
   nabanggit mo na alam mo ang tungkol sa rabies disease at kung ano ang nangyayari sa mga taong nakakuha nito, kapag hindi mo nakumpleto ang iyong mga bakuna, natakot ka ba?

10. Ano sana ang nakatulong o nakahikayat sa iyo na bumalik para sa iyong mga dosis?
    Probes: Kawani, impormasyon, karanasan sa pagbibigay ng bakuna, paalala

11. Ano ang tingin mo sa pagpapadala ng klinika ng mga paalala tungkol sa bakuna sa rabies?
    Probes: Matutuwa ka bang makatanggap ng text message o tawag para paalalahanan? Alin ang mas pipiliin mo? Iyon ba ay makakatulong sana? May gusto ka bang uri ng mensahe?

12. (*Explain rabies can lead to death, the importance of finishing vaccines. If phone interview, if they come to SLH they can receive PHP100 transport assistance)/ (Ipaliwanag ang rabies ay maaaring mauwi sa kamatayan, ang kahalagahan ng pagtatapos ng mga bakuna, kung sila ay dumating sa SLH maaari silang makatanggap ng PHP100 na transport assistance).*
    Ngayong alam mo na ang rabies ay maaaring humantong sa kamatayan, maaari ka bang pumunta sa SLH o pumunta sa isa pang ABTC para kumpletuhin?

10.2.5 Study 4: Contact Survey

Screening

Record ID	_____
Age	_____
Date	_____
Is the patient a potential participant?	◯ Yes ◯ No
Did the patient participate?	◯ Yes ◯ No
If No, what was the reason?	_____

Demographics

Study ID	_____
Date of interview	_____
Referring participant from Study 3 participant ID no.	_____ (prefilled)
Name of Referral	_____ (prefilled but reconfirm)
Phone number	_____ (prefilled)

We're calling you because you may have had a rabies exposure recently. A rabies exposure is a bite or scratch, of eating mammals like dogs, cats or rodents that may have rabies.

Have you or your ward been bitten or scratched by an animal recently?	◯ Yes ◯ No
Did you receive a rabies vaccine after exposure?	◯ Yes ◯ No
Did you or your ward go to a clinic, hospital or ABTC?	◯ Yes ◯ No
If yes, were you recommended a rabies vaccine?	◯ Yes ◯ No

DEMOGRAPHICS

Are you the patient?	◯ Yes ◯ No
If the respondent is not the patient, relationship to the patient?	◯ Parent ◯ Grandparent ◯ Nanny ◯ Sibling ◯ Other Guardian

City of Residence	◯ Manila City ◯ Quezon City ◯ Caloocan City ◯ Las Pinas City ◯ Makati City ◯ Malabon City ◯ Mandaluyong City ◯ Marikina City ◯ Muntinlupa City ◯ Navotas City ◯ Paranaque City ◯ Pasay City ◯ Pasig City ◯ Pateros ◯ Quezon City ◯ San Juan City ◯ Taguig City ◯ Valenzuela City ◯ Unknwon ◯ Outside Metro Manila
Barangay	_____
How long does it take you to get to SLH	_____
Gender	◯ Male ◯ Female ◯ Prefer not to answer
Date of birth	_____
Age	_____
Educational Status	◯ No formal education ◯ Primary School ◯ Secondary School ◯ Bachelor's Degree ◯ Post Graduate Degree / Master's / Doctorate degree ◯ Prefer not to answer
Monthly income in PHP	◯ < 5,000 ◯ 5,000-10,000 ◯ 10,000-15,000 ◯ 15,000-20,000 ◯ >20,000
Homeowner?	◯ Yes ◯ No
If not, how much do you pay for rent?	_____

Rabies Risk and Bite Characteristics

Do you own pets?	◯ Yes ◯ No
What type of pet?	☐ Dog ☐ Cat ☐ Other mammal ☐ Other animal
If Dog, Is it vaccinated?	◯ Yes ◯ No
When did it received its last vaccination?	_____

A rabies is a bite or scratch, of eating mammals like dogs, cats or rodents that may have rabies.

What type of exposure did you have?	☐ Scratch ☐ Bite ☐ Multiple bites ☐ Consumption
Where is the exposure site?	☐ Head ☐ Arms ☐ Torso ☐ Upper legs ☐ Lower legs
When did the exposure occur?	_____
Is the animal a pet or stray?	◯ Participant's pet ◯ Other's pet ◯ Stray
If pet, do you know the vaccination status of the pet?	◯ Vaccinated (within the last 1 year) ◯ Unvaccinated ◯ Vaccination status unknown
Is the animal alive?	◯ Yes ◯ No ◯ Unknown
Did you carry out any treatment for the wound?	☐ Wound Washing ☐ Tandok ☐ Bleeding the wound ☐ Medical Consultation ☐ Other ☐ None
Other:	_____

Have you had a rabies vaccine prior to this rabies exposure?	◯ Yes ◯ No
Was it before or after a rabies exposure?	◯ Preexposure ◯ Postexposure
When was the vaccine received?	_____
How many doses were received?	◯ 1 ◯ 2 ◯ 3 ◯ 4+
How far (in minutes) is the closest ABTC to your house?	_____

Perceived Severity

	Death	Very Serious	Not very serious	Not serious at all	Don't know
How serious would it be for someone to get rabies?	◯	◯	◯	◯	◯

Perceived Susceptibility

Do you know someone who had rabies?	◯ Yes ◯ No

How likely do you think it would be for someone to get rabies after an animal bite or scratch?

	Very likely	Likely	Not likely	Impossible	Don't know
Dog bite	◯	◯	◯	◯	◯
Dog scratch	◯	◯	◯	◯	◯
Bat contact	◯	◯	◯	◯	◯
Cat bite	◯	◯	◯	◯	◯
Cat scratch	◯	◯	◯	◯	◯

Perceived Benefits

How much do you agree or disagree with this statement

	Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree
"Vaccines are important for children to have"?	◯	◯	◯	◯	◯

For each of these vaccines, How much do you agree that vaccines are effective?

	Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree
Rabies Vaccine	○	○	○	○	○
Measles Vaccine	○	○	○	○	○
Tetanus Vaccine	○	○	○	○	○
Dengue Vaccine	○	○	○	○	○
Covid-19 Vaccine	○	○	○	○	○

For each of these vaccines, How much do you agree that vaccines are safe?

	Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree
Rabies Vaccine	○	○	○	○	○
Measles Vaccine	○	○	○	○	○
Tetanus Vaccine	○	○	○	○	○
Dengue Vaccine	○	○	○	○	○
Covid-19 Vaccine	○	○	○	○	○

Have you received covid-19 vaccine?

- ○ Yes
- ○ No
- ○ Medically exempt

How many doses of covid-19 vaccine have you received?

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4

How much do you trust each of the following?

	A lot	Some	Not much	Not at all	Don't know
Doctors	○	○	○	○	○
Scientists	○	○	○	○	○
Department of Health	○	○	○	○	○
News media (TV, radio, newspapers)	○	○	○	○	○
Internet and social media	○	○	○	○	○

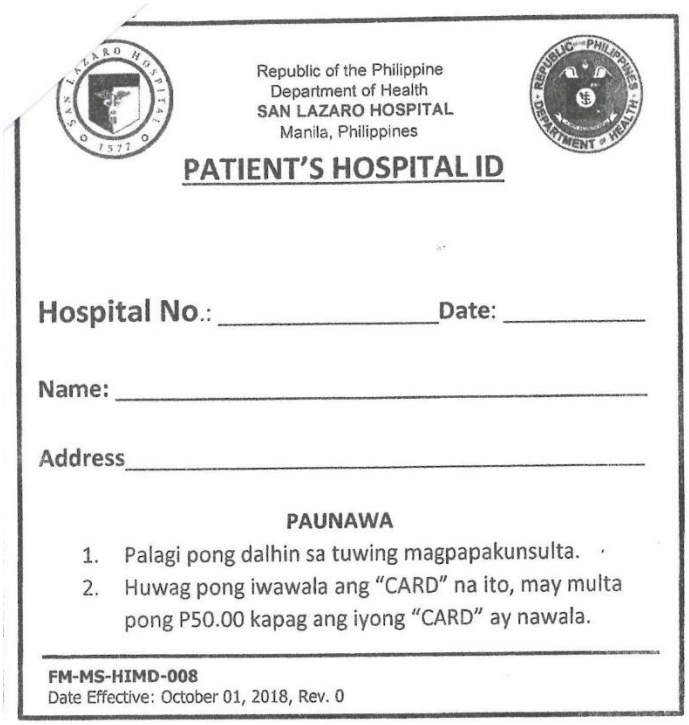
Why did you not receive a rabies vaccination after this bite?

_____

Do you know if anyone in your community was bitten by a dog and did not seek medical care, go to an ABTC, or get a rabies vaccine?	◯ Yes ◯ No
If yes, were they bitten by the same dog?	◯ Yes ◯ No
Could you call or send a message asking if they are willing to participate in the study?	◯ Yes ◯ No
Name of referral	_____
Phone number of contact	_____

10.3 Forms and Flyers in Use at SLH ABTC

1. Patient's Hospital ID card



Republic of the Philippine
Department of Health
SAN LAZARO HOSPITAL
Manila, Philippines

PATIENT'S HOSPITAL ID

Hospital No.: _____ **Date:** _____

Name: _____

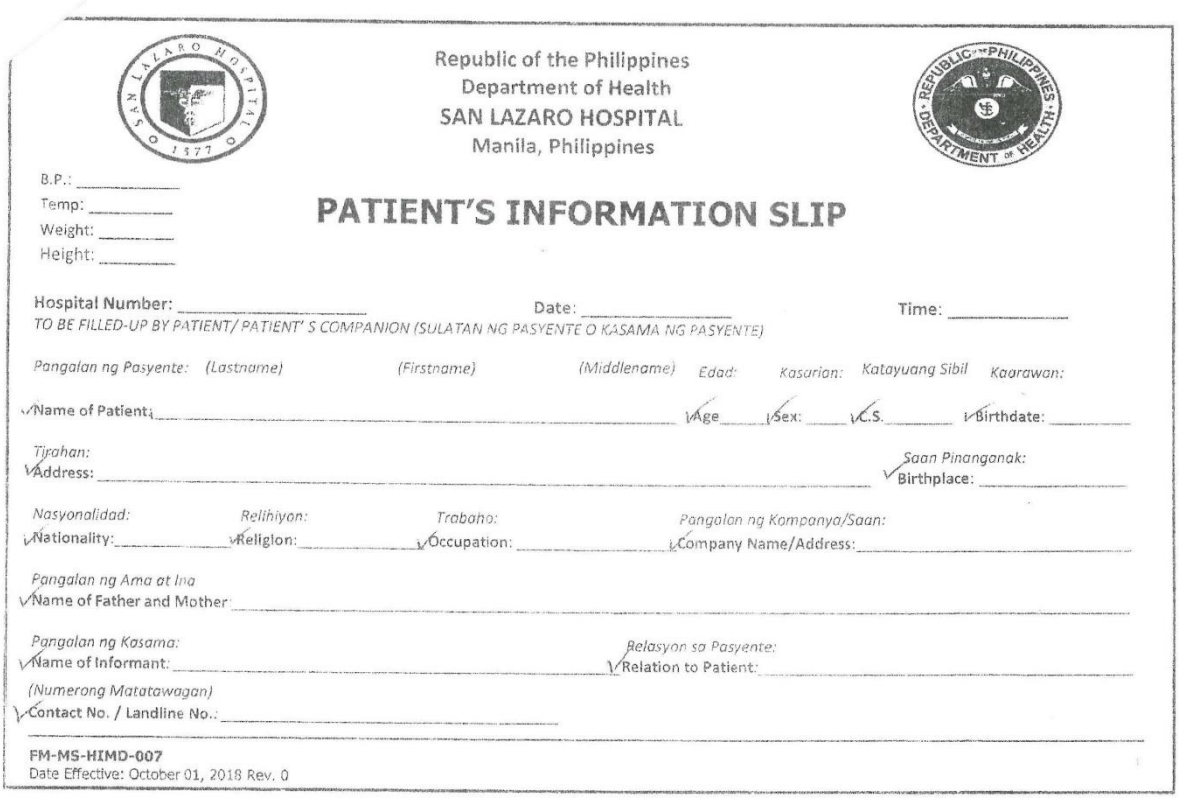
Address _____

PAUNAWA

1. Palagi pong dalhin sa tuwing magpapakunsulta.
2. Huwag pong iwawala ang "CARD" na ito, may multa pong P50.00 kapag ang iyong "CARD" ay nawala.

FM-MS-HIMD-008
Date Effective: October 01, 2018, Rev. 0

2. Patient's Information Slip



Republic of the Philippines
Department of Health
SAN LAZARO HOSPITAL
Manila, Philippines

B.P.: _____
Temp: _____
Weight: _____
Height: _____

PATIENT'S INFORMATION SLIP

Hospital Number: _____ Date: _____ Time: _____
TO BE FILLED-UP BY PATIENT/ PATIENT' S COMPANION (SULATAN NG PASYENTE O KASAMA NG PASYENTE)

Pangalan ng Pasyente: *(Lastname)* *(Firstname)* *(Middlename)* *Edad:* *Kasarian:* *Katayuang Sibil* *Kaarawan:*

Name of Patient: _____ Age ____ Sex: ____ C.S. ____ Birthdate: _____

Tirahan:
Address: _____ *Saan Pinanganak:* Birthplace: _____

Nasyonalidad: *Relihiyon:* *Trabaho:* *Pangalan ng Kompanya/Saan:*
Nationality: _____ Religion: _____ Occupation: _____ Company Name/Address: _____

Pangalan ng Ama at Ina
Name of Father and Mother: _____

Pangalan ng Kasama: *Relasyon sa Pasyente:*
Name of Informant: _____ Relation to Patient: _____

(Numerong Matatawagan)
Contact No. / Landline No.: _____

FM-MS-HIMD-007
Date Effective: October 01, 2018 Rev. 0

3. Animal and Human Bite Data Sheet. Colloquially – “blotter sheet”

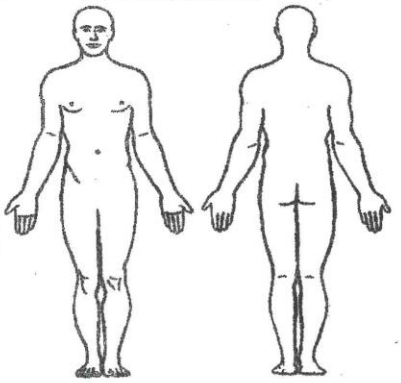
Republic of the Philippines
Department of Health
SAN LAZARO HOSPITAL
Manila, Philippines

Informant ☐ Self (Patient/Injured) ☐ Family member ☐ Police ☐ Others Specify: _____

ANIMAL AND HUMAN BITE DATA SHEET

Printed reg info
Name

HISTORY OF BITE
TYPE OF EXPOSURE: ☐ NON-BITE ☐ BITE
Site of Bite (also illustrated using the drawing)
☐ Head ☐ Chest ☐ Upper Extremities
☐ Face ☐ Back ☐ Lower Extremities
☐ Neck ☐ Abdomen ☐ Others (specify)
Date of Injury ___/___/___ (mm/dd/yyy) Time of Injury _____ (am/pm)
Nature of Injury/ies:
Multiple injuries? ☐ Yes ☐ No
Check all applicable, indicate in the black space opposite each type of injury the body location affected and other details
☐ Abrasion ☐ Avulsion
☐ Burn (Degree of Burn & Extent of Body Surface involv Degree: 1 2 3 4 Site: _____
☐ Concussion ☐ Contusion
☐ Fracture
☐ Closed type (ex. Comminuted, depressed fracture)
☐ Open type (ex. Compound, infected fracture)
☐ Open wound/Laceration ☐ Trauma ☐ Others:



External Cause/s of Injury/ies
☐ Bite/Sting, Specify animal/insect
☐ Chemical Substance, specify (applied to bite site)
Place of Occurrence ___ Home ___ School ___ Road ___ Videoke Bars ___ Others
Activity of the patient at the time of incident ___ Sports ___ Leisure ___ Others ___ Unknown
Status upon reaching Facility/Hospital ___ Dead on Arrival
___ Alive : If alive, please check if: ___ Conscious ___ Unconscious
Disposition ___ Admitted ___ Treated & Sent Home ___ HAMA ___ Absconded
___ Transferred to another facility/Hospital, specify:
Outcome ___ Improved ___ Unimproved
Circumstance of Bite ☐ Provoked ☐ Unprovoked

ANIMAL PROFILE
Species ☐ Dog ☐ Cat ☐ Others (Specify)
Clinical Status ☐ Healthy ☐ Sick ☐ Died ☐ Killed ☐ Brain exam done ☐ No Brain Exam done ☐ Unknown
Anti-Rabies Vaccination Status of Animal: ☐ Immunized, when: _____ ☐ None ☐ Unknown
Ownership Status: ☐ Pet ☐ Neighbor ☐ Stray
Diagnosis: _____

Category of Bite Management: ☐ Category 1 ☐ Category 2 ☐ Category 3
Any History of Allergy: _____
Maintenance Medications _____

MD Signature over trodat

Conforme: Pinahihintulutan ko ang doktor at nars ng San Lazaro Hospital na gamutin at gawin ang kaukulang lunas na makabubuti sa sakit o kondisyon ko o ng aking pasyente. Naunawaan ko ang paliwanag ng doktor at nars sa magiging epekto ng gamot at posibleng komplikasyon dulot nito.

Lagda ng Pasyente/ Bantay

Lagda ng Saksi

Patient Immunization

A. DPT Immunization ☐ Complete Year Given(last dose) _____ ☐ Incomplete No. of doses given _____ ☐ None

Previous	☐ Active	☐ Passive
No. of doses given	☐ Toxoid	☐ SKIN TEST Time Tested _____ Time Read _____ Result _____ MD Signature over trodat
Year last dose given	Date / RN Signature over trodat TT_1 _____ TT_2 _____ TT_3 _____	Dose _____ "U" Date Given _____ RN Signature over trodat ☐ TIG Dose _____ "U" Date Given _____ RN Signature over trodat

☐ Active Date Given _____ Where: _____ ☐ None

☐ Passive Date Given _____ Where: _____

Current Anti Rabies Immunization

☐ Active ☐ Pre-Exposure Prophylaxis ☐ (Previously Immunized/PEP)

☐ PVRV ☐ PCEC

☐ ID ☐ TRC-ID (2-2-2-0-1-1) ☐ Others, specify

☐ IM ☐ Zagreb (2-1-1)

SCHEDULE DATES OF IMMUNIZATION

DATE	DATE	DATE	RN Signature over trodat
D_0 _____	D_0 _____	D_0 _____	_____
D_3 _____	D_3 _____		_____
D_7 _____	D_7 _____	D_7 _____	_____
D_{30} _____	D_{14} _____		_____
D_{90} _____	D_{28} _____	D_{21} _____	_____

☐ Passive

☐ SKIN TEST

Time Read _____

Result _____

_____ MD Signature over Trodat

Date Given _____

_____

☐ HRIG

Dose _____

Date Given _____

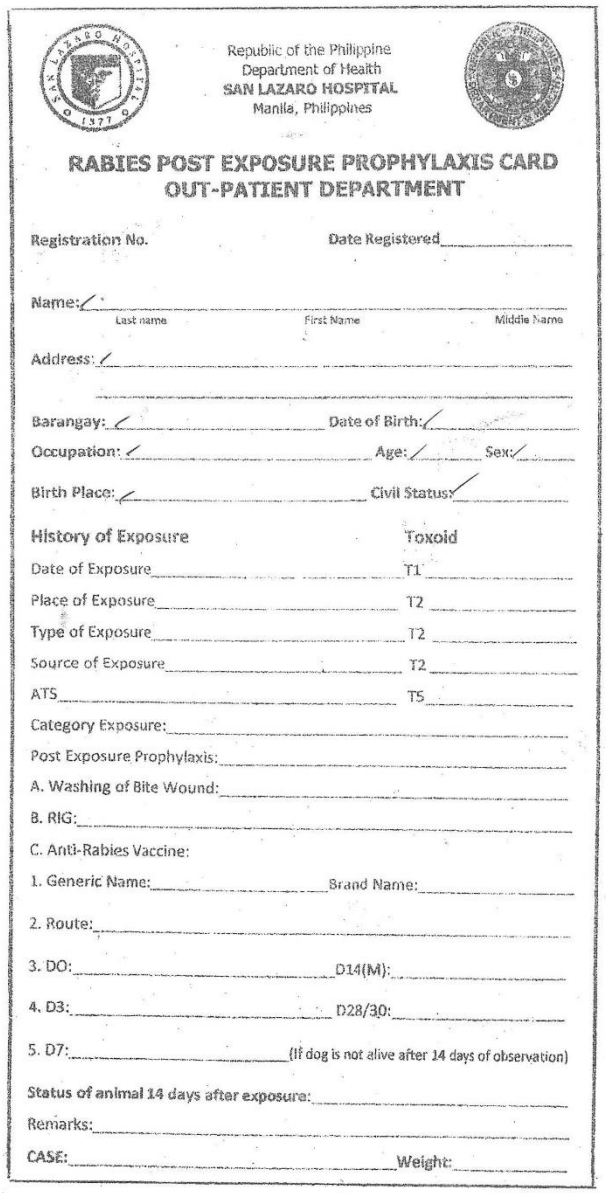
_____ RN Signature over trodat

_____ Local Infiltration done

☐ Sutured ☐ Unsutured

Date of Follow-up	Findings/Adverse Reaction	Management	MD Signature over trodat

4. Post-Exposure Prophylaxis card



Republic of the Philippine
Department of Health
SAN LAZARO HOSPITAL
Manila, Philippines

RABIES POST EXPOSURE PROPHYLAXIS CARD
OUT-PATIENT DEPARTMENT

Registration No. Date Registered

Name: Last name First Name Middle Name

Address:

Barangay: Date of Birth:

Occupation: Age: Sex:

Birth Place: Civil Status

History of Exposure	Toxoid
Date of Exposure	T1
Place of Exposure	T2
Type of Exposure	T2
Source of Exposure	T2
ATS	T5

Category Exposure:

Post Exposure Prophylaxis:

A. Washing of Bite Wound:

B. RIG:

C. Anti-Rabies Vaccine:

1. Generic Name: Brand Name:

2. Route:

3. DO: D14(M):

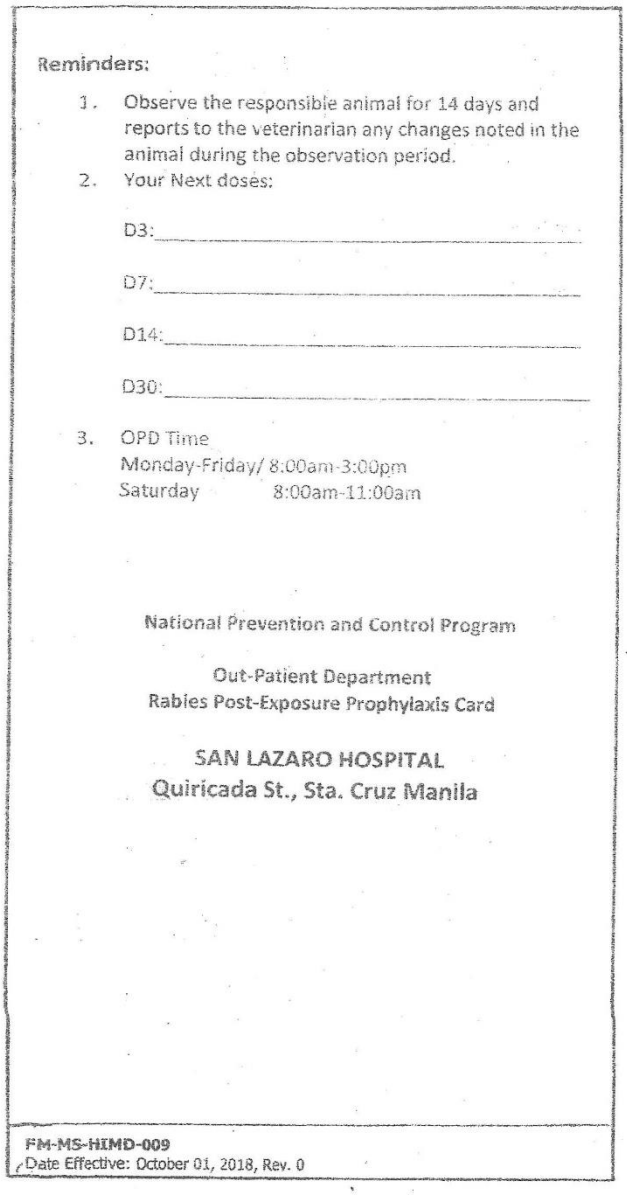
4. D3: D28/30:

5. D7: (If dog is not alive after 14 days of observation)

Status of animal 14 days after exposure:

Remarks:

CASE: Weight:



Reminders:

1. Observe the responsible animal for 14 days and reports to the veterinarian any changes noted in the animal during the observation period.
2. Your Next doses:

   D3:

   D7:

   D14:

   D30:

3. OPD Time
   Monday-Friday/ 8:00am-3:00pm
   Saturday 8:00am-11:00am

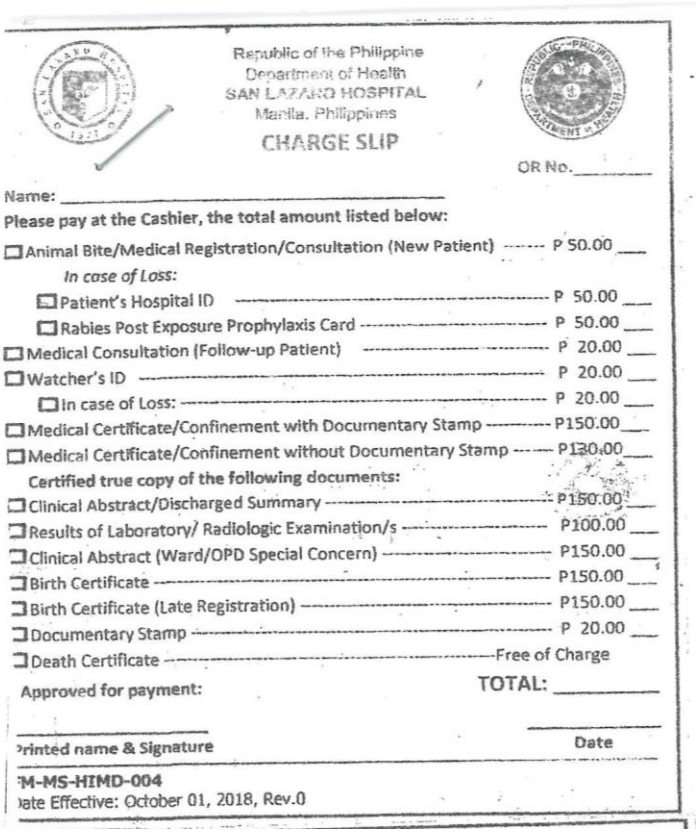
National Prevention and Control Program

Out-Patient Department
Rabies Post-Exposure Prophylaxis Card

SAN LAZARO HOSPITAL
Quiricada St., Sta. Cruz Manila

FM-MS-HIMD-009
Date Effective: October 01, 2018, Rev. 0

5. Charge Slip



Republic of the Philippine
Department of Health
SAN LAZARO HOSPITAL
Manila, Philippines

CHARGE SLIP

OR No._____

Name: _____

Please pay at the Cashier, the total amount listed below:

- ☐ Animal Bite/Medical Registration/Consultation (New Patient) ------- P 50.00 ___
  - *In case of Loss:*
  - ☐ Patient's Hospital ID ---------- P 50.00 ___
  - ☐ Rabies Post Exposure Prophylaxis Card ---------- P 50.00 ___
- ☐ Medical Consultation (Follow-up Patient) ---------- P 20.00 ___
- ☐ Watcher's ID ---------- P 20.00 ___
  - ☐ In case of Loss: ---------- P 20.00 ___
- ☐ Medical Certificate/Confinement with Documentary Stamp ---------- P150.00 ___
- ☐ Medical Certificate/Confinement without Documentary Stamp ------ P130.00 ___

Certified true copy of the following documents:

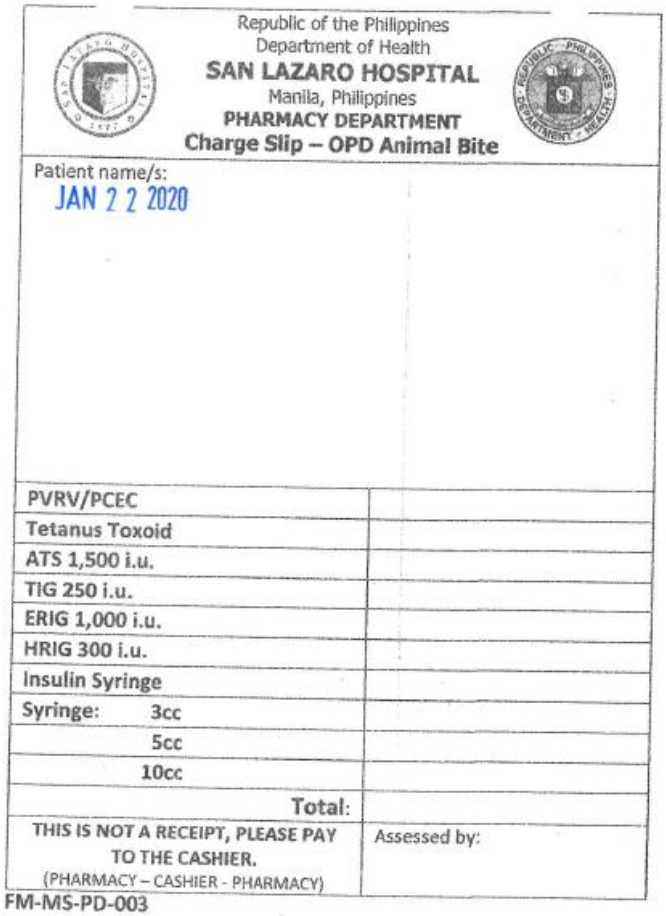
- ☐ Clinical Abstract/Discharged Summary ---------- P150.00 ___
- ☐ Results of Laboratory/ Radiologic Examination/s ---------- P100.00 ___
- ☐ Clinical Abstract (Ward/OPD Special Concern) ---------- P150.00 ___
- ☐ Birth Certificate ---------- P150.00 ___
- ☐ Birth Certificate (Late Registration) ---------- P150.00 ___
- ☐ Documentary Stamp ---------- P 20.00 ___
- ☐ Death Certificate ----------Free of Charge

Approved for payment: **TOTAL:** _____

_____ _____

Printed name & Signature **Date**

FM-MS-HIMD-004
Date Effective: October 01, 2018, Rev.0



Republic of the Philippines
Department of Health
SAN LAZARO HOSPITAL
Manila, Philippines
PHARMACY DEPARTMENT
Charge Slip – OPD Animal Bite

Patient name/s:
JAN 2 2 2020

PVRV/PCEC	
Tetanus Toxoid	
ATS 1,500 i.u.	
TIG 250 i.u.	
ERIG 1,000 i.u.	
HRIG 300 i.u.	
Insulin Syringe	
Syringe: 3cc	
5cc	
10cc	
Total:	
THIS IS NOT A RECEIPT, PLEASE PAY TO THE CASHIER. (PHARMACY – CASHIER - PHARMACY)	Assessed by:

FM-MS-PD-003
Date Effective: January 21, 2019, Rev. 0

6. Rabies Information Leaflets

TANDAAN:

Courtesy: Google Images

Ang rabis ay
NAKAMAMATAY
subalit maaring
MAIWASAN!
Pabakunahan ang
mga alagang aso.

Para sa karagdagang impormasyon, huwag mag-atubiling kumontak sa

SAN LAZARO HOSPITAL
PUBLIC HEALTH UNIT

@slhpho

slhpho@gmail.com

732-3776 to 78 loc.157

2019

MGA KATOTOHANAN UKOL SA RABIS

Courtesy: Google Images

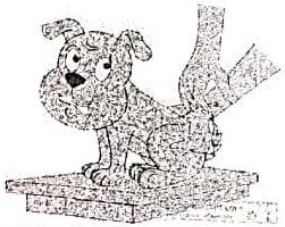
MGA KATOTOHANAN UKOL SA RABIS AYON SA WHO *(WORLD HEALTH ORGANIZATION)*

1. Ang **Rabis** ay isang sakit mula sa ***Rhabdovirus*** na hugis bala at naisasalin sa tao sa pamamagitan ng kagat o kalmot na may bahid ng laway ng hayop.

Courtesy: Google Images

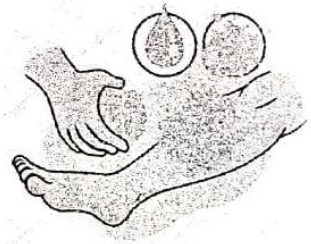
2. **99%** kaso ng rabis ay mula sa kagat ng asong ulol. Sa Pilipinas, maari ding makuha ang rabis sa kagat o kalmot ng ulol na pusa.
3. Halos kalahati (40%) ng kaso ng rabis ay mga batang nasa 15 taong gulang pababa, subalit bihira itong napapahayag.
4. Ang daga ay hindi makapagsasalin ng rabis kapag nakagat ang tao.
5. Ang garantisadong paraan upang malabanan ang rabis ay ang mga sumusunod:

- pagpapabakuna sa mga alagang hayop
- iwasang makagat ng hayop



Courtesy: Google Images

6. Agaran at wastong paglilinis ng sugat sa pamamagitan ng malinis na tubig at sabon sa loob ng **10-15 minuto.**



Courtesy: Google Images

7. Mga mataas na potensyal ng rabis *exposure* na nangangailangan ng agaran at kumpletong bakuna:

- nagkasakit o namatay ang hayop sa loob ng **10-14 na araw** mula nang makagat
- ang kagat ay sa leeg, mukha, at ulo
- ligaw o galang hayop at hindi na maaaring obserbahan ng 10-14 na araw
- katutubo *(endemic)* ang rabis sa lugar at walang bakuna ang hayop laban sa rabis

8. Kung mataas ang potensyal ng rabis *exposure*, pumunta agad sa pinakamalapit na pagamutan o ospital para mabigyan ng bakuna kontra rabis.

MGA SINTOMAS NG RABIS SA TAO

Agarang mga sintomas:

- pangangati, pamamanhid, pangingilig ng sugat na kinagat ng hayop
- parang trangkaso (lagnat, sakit ng ulo, panghihina ng katawan)

Courtesy: Google Images

Pang-huling mga sintomas:

- insomya/pagkalito/pagkabalisa
- matinding paglalaway
- takot sa hangin *(aerophobia)*
- takot sa tubig *(hydrophobia)*
- pagka-paralisa
- pagkamatay

WHO ARE MOST AT RISK FOR RABIES INFECTION?

Pet owners[1]

Children[2,3]

Animal handlers[4]

WHAT IS RABIES?

It is a virus that attacks the central nervous system, which causes a debilitating disease that ultimately leads to death, if not treated immediately.[1]

IT IS TRANSMITTED IN SALIVA.

Infected dogs, cats, rats, bats, etc., infect others often through a bite, or scratch, or licks on open wounds or broken skin. Initially, itching or pain is felt on the bite, followed by 2-4 days of flu-like symptoms.[1]

IT TAKES TIME FOR SYMPTOMS TO APPEAR.

The victim appears healthy, as the virus makes its way from the site of infection to the brain. Anywhere from a few weeks to several months, the real symptoms become apparent - by which time, it takes but a few days before death occurs.[1]

SYMPTOMS OF RABIES:

- Confusion, hallucinations[1]
- Irritability, aggression[1]
- Anxiety, hyperactivity, insomnia[1]
- Fear of water, which causes throat spasms[1]
- Excessive salivation[1]

CHILDREN ARE AT HIGHER RISK.

40% of reported bites are on children 15 years old and below.[2] They are at greater risk of rabies exposure than adults because they:

- Tend to play more with animals[1]
- May receive bites of greater severity[1]
- May not report bites immediately[1]

CONSEQUENCES OF RABIES

- Trauma from exposure to the fatal disease[6]
- Lost productivity and income from time and travel spent on multiple visits to the doctor[6]
- Cost of Rabies Immune Globulin and Rabies Vaccines[6]
- Death[6]

RABIES IS A REAL THREAT.

- Rabies is fatal[7]
- Rabies is endemic in the Philippines[8]
- 200 individuals have died due to rabies infection in 2013[2,5]

YOU COULD BE NEXT.

You'll never know when an animal would bite, but your chances of surviving infection are improved with preventive measures, prior to any risk of exposure.

- Have yourself vaccinated against rabies infection prior to any animal contact.[1]
- Have your pets vaccinated against rabies infection.[7]
- Be sensitive to an animal's body language, especially when petting, feeding, or just being in close contact with any animal.[7]
- Do not consume the meat of animals suspected of rabies infection.[1] (If having done so, seek medical help **immediately**.)

BILIS. LABANAN ANG RABIS!

RABIES INFECTION CAN BE PREVENTED. VISIT YOUR DOCTOR TODAY!

BILIS. LABANAN ANG RABIS!

Citations:

1. "Frequently Asked Questions on Rabies." World Health Organization Regional Office for South-East Asia. New Delhi, India. 2013.
2. "National Rabies Prevention and Control Program, Manual of Operations." Department of Health. Manila, Philippines. 2012. ISBN 978-971-0569-33-5
3. "Advisory Committee on Immunization Practices Human Rabies Prevention." Centers for Disease Control and Prevention. USA. 2008. http://www.cdc.gov/mmwr/PDF/rr/rr5703.pdf. Accessed December 2014.
4. "Expert Consultation on Rabies, Second Report." World Health Organization. 2013 http://apps.who.int/iris/bit-stream/10665/85346/1/9789240690943_eng.pdf. Accessed September 2015.
5. "Anti-Rabies Vaccines Can Now Be Availed For Free In ABTCs Nationwide, Says DOH." A. Macolor. Kicker Daily News. 06 January 2016.
6. "Estimating the Global Burden of Endemic Canine Rabies." K. Hampson, L. Coudeville, T. Lembo, et al. US National Library of Medicine, National Institutes of Health. 2015. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4400070/. Accessed March 2016.
7. "Rabies: The Facts." World Health Organization. 2015. http://www.who.int/topics/rabies/rabies-infographic-2015.jpg?ua=1. Accessed February 2016.
8. "Rabies, countries or areas at risk." World Health Organization. 2013. Available at: http://gamapserver.who.int/mapLibrary/Files/Maps/Global_Rabies_ITHRiskMap.png

A health service message brought to you by GSK.

gsk

GlaxoSmithKline Philippines Inc.
2266 Chino Roces Ave, Makati City

For further information, please consult your doctor.
Adverse events? Please e-mail us: **ph.safety@gsk.com** or **contact 0917 889 0640**
For product complaints, contact **0917 889 7050**
PH/RIR/0009/16a March 2016

NOVARTIS MARKETLINK

10.4 Research Ethics Approvals

	SAN LAZARO HOSPITAL RESEARCH ETHICS AND REVIEW UNIT **FORM 2.11**	VERSION NO. 1 EFFECTIVITY DATE: **MAY 28, 2018**

CERTIFICATE OF APPROVAL

Date January 21, 2022

This is to certify that the following protocol and related documents have been granted approval by the SLH-RERU for implementation

RERU Protocol No.	SLH-RERU-2021-004-I	Sponsor Protocol No	
Principal Investigator/s	Oladeji Oloko, PhD/ Ferdinand De Guzman, MD	Sponsor	Nagasaki University-London School of Hygiene and Tropical Medicine (LSHTM)
Title	"Rabies Post-Exposure Prophylaxis in the Philippines: Understanding factors associated with vaccine uptake and exploring interventions to improve adherence"		
Protocol Version No.	Version 5	Version Date	January 14, 2022
ICF Version No.	Version 5	Version Date	January 14, 2022
Other documents	N/A		N/A
Members of research team	Chris Smith, Ana Ria Sayo Ryan Jean Ceralvo, Pauline Paterson, Kristal An Agrupis, Koya Ariyoshi		
Study sites	SAN LAZARO HOSPITAL		

Type of review	☐ Expedited ☒ Full board Meeting date: January 19, 2022	Duration of Approval From (date) To JANUARY 21, 2022 JANUARY 21, 2023	Frequency of continuing review 1 YEAR

Date of Approval	Recommending Approval	Approved by

SAN LAZARO HOSPITAL RESEARCH ETHICS AND REVIEW UNIT **FORM 2.11**		VERSION NO. 1 EFFECTIVITY DATE: **MAY 28, 2018**

01/21/2022	Dr. Grace Go/Dr. Michael San Juan/ Dra Daisy Tagarda/Atty. Frances Mae Ontalan	[redacted] Jay Ron O. Padua, MD,FPPS,FPIDSP

*See investigator's responsibilities after approval (next page)

Investigator Responsibilities after Approval:

- Submit document amendments for RERU approval before implementing them
- Submit SAE and SUSAR reports to the SLH-RERU within 7 days
- Submit progress report every 6 months
- Submit final report after completion of protocol procedures at the study site
- Report protocol deviation/ violation
- Comply with all relevant international and national guidelines and regulations
- Abide by the principles of good clinical practice and ethical research

Received by: _____

Name _____

Signature _____ Date _____

Note:
All concerns, queries shall be coursed thru the SLH-RERU office thru email, fax or memo. Please refer to contact details below:
Name of Secretariat:_____
email ad: slh.iso.reru@gmail.com
tel/fax no.: 310-32-11

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

LSHTM

29 October 2021

Dear Miss Oloko

Study Title: Rabies Post-Exposure Prophylaxis in the Philippines: Understanding factors associated with vaccination and exploring interventions to improve uptake.

LSHTM Ethics Ref: 22718

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Investigator CV	Chris Smith CV	06/01/2021	1
Other	Chris Smith GCP certificate	18/01/2021	1
Other	Research Ethics Pauline Paterson	20/01/2021	1
Investigator CV	Oladeji Oloko CV	31/01/2021	1
Investigator CV	Pauline Paterson CV	31/01/2021	1
Other	Oladeji Oloko GCP Certificate	04/02/2021	1
Information Sheet	PIS & Consent Forms Eng-Tagalog	28/02/2021	1
Protocol / Proposal	Rabies PEP Protocol for LSHTM	28/02/2021	1
Protocol / Proposal	Data collection forms	28/02/2021	1
Protocol / Proposal	PIS & Consent	28/02/2021	1
Other	Oladeji Oloko Research Ethics	31/03/2021	1
Covering Letter	Cover Letter	09/09/2021	1
Protocol / Proposal	LSHTM Rabies PEP Protocol Resubmission	09/09/2021	2
Covering Letter	Cover Letter	19/10/2021	2

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]

Professor Jimmy Whitworth
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide