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An intersectoral approach to enhance surveillance and guide rabies control and elimination programs

by
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Abstract

Rabies is a viral zoonotic disease causing horrific neurological symptoms inevitably leading to death without prompt administration of post-exposure prophylaxis (PEP) to prevent infection. While any mammal can be infected by and transmit rabies, almost 99% of the estimated 59,000 human deaths per year are due to bites from rabid dogs, with the vast majority occurring in Asia and Africa. Through mass dog vaccinations starting in the 1920s, rabies has been successfully eliminated from domestic dog populations in practically all high-income countries. Yet, many low- and middle-income countries (LMICs) are still endemic and face extensive challenges controlling rabies and achieving elimination.

Strengthening surveillance through integrated intersectoral methods has been an important component of the *Zero by 30* global strategy to eliminate human deaths from dog-mediated rabies by 2030. Similar to other neglected tropical diseases, only a small percentage of human and animal rabies cases are captured in surveillance at the local level, then go on to be reported in official national and international statistics. This lack of detection and underreporting has resulted in suboptimal data quality that conceals the true magnitude of the burden of rabies, leading to a cycle of neglect by reducing advocacy, funding, and stakeholder engagement. Hence, surveillance must be sufficiently enhanced to monitor, evaluate, and inform rabies control efforts to support LMICs to achieve elimination.

This thesis aims to critically review and evaluate the One Health approach, Integrated Bite Case Management (IBCM), as a cost-effective method to enhance rabies surveillance and guide control and elimination programs in LMICs, with a particular focus on a case study of IBCM implementation in the Philippines. The thesis is presented in a series of five chapters, starting with a general introduction (Chapter 1), followed by three standalone data chapters (Chapters 2, 3 & 4), and concluding with a general discussion (Chapter 5).

IBCM is a current gold standard surveillance method advocated by WHO and other international organizations. Yet, as a relatively novel One Health approach, there is still little understood about the implementation of IBCM in practice. In Chapter 2, I examined how IBCM is conceptualized by experts in the field, exploring variation in its operationalization in different epidemiological and geographical contexts. Findings from this study highlighted the diversity of how IBCM can be organized within existing government systems/sectors and demonstrated it is not a one-size-fits-all approach. Contextual features of each location influenced the success of delivery and the potential impact of IBCM, with the issue of sustainability identified as one of the greatest challenges. For successful development and implementation of IBCM programs, this study recommends that more guidance is provided for health workers receiving bite patients on assessing rabies-risk, and for stakeholders and practitioners on how to tailor IBCM to fit the local context.

In Chapter 3, I explored this topic in more depth through the evaluation of a three-year (January 2020 to December 2022) implementation study of IBCM in Oriental Mindoro province, Philippines. Using a mixed methods process evaluation, I assessed the feasibility and fidelity of effective delivery of IBCM, and how protocols were adapted to the context over the course of the study. The evaluation showed that the initial protocols envisioning trained government staff would uptake IBCM activities were not feasible due to implementation barriers. However, following adaptations made by the project team and participants, including adjustments for the COVID-19 pandemic, IBCM was delivering more effectively in 2021 and 2022. The findings concluded that, if implemented effectively, IBCM showed great promise as a strategy to enhance rabies surveillance in the Philippines, with evidence from the study providing key lessons for the adaptation and scale-up of IBCM to additional provinces in the Philippines.

In Chapter 4, I used data collected from enhanced IBCM surveillance in Oriental Mindoro province from the implementation study discussed in Chapter 3. This quantitative data was used to develop an adapted probabilistic decision tree model used to estimate the burden of rabies, evaluate surveillance performance, and assess the impact of current rabies prevention practices. Results from this study estimated a high incidence of bite patient presentations to health facilities (1,160/100,000 persons/year), with <2% deemed high-risk for rabies exposures

(<25/100,000 persons/year) and an average of 71.4% of probable rabies-exposed patients seeking PEP. Routine surveillance confirmed <1% of circulating animal cases, whereas IBCM resulted in a fivefold increase in detection. The model estimated that between 275 to 838 dogs developed rabies; 18 to 28 deaths were averted by PEP; and total costs of over $535,385 USD per year, i.e. $16,730-38,240 USD per death averted, in Oriental Mindoro province. These findings highlight that current PEP practices in the Philippines are not cost-effective without concurrent strengthened risk-based surveillance to reduce the indiscriminate use of PEP. The study concludes that integrating IBCM into national policy has the potential to guide PEP administration to reduce unnecessary expenditure on PEP and inform rabies control measures.

Overall, this thesis exemplifies the value of enhancing rabies surveillance using a One Health approach to achieve *Zero by 30* rabies elimination goals. Yet, the development and implementation of IBCM must be carefully considered and planned to ensure the effective delivery of IBCM activities leading to desired outputs and outcomes. With more guidance provided by international organizations to streamline protocols and procedures, the IBCM approach has the potential to be a key component of national strategies to monitor and evaluate the progress of rabies control efforts, verify elimination, and promptly detect incursion events.

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Author's Declaration

I declare that the contents presented in this thesis are the result of original research conducted and composed by the author, Catherine Swedberg, except where otherwise stated. Where work has been derived from collaboration with others, every effort has been made to indicate this. Chapters 2, 3 & 4 in this thesis have been produced as stand-alone manuscripts for publication (or already published) along with co-authorship from my supervisors and research project team. My contribution to each thesis chapter is indicated below:

Chapter 1: I solely wrote the first introduction chapter with edits and reviews conducted by my supervisors KH and NRC.

Data Chapter 2: For this chapter, I conceptualized the study design and methodology; collected and transcribed all interviews; conducted the initial analysis of data; wrote the original draft; and reviewed/edited the final draft. My supervisors KH and NRC oversaw the study design; conceptualization; methodology; interpretation of results; and writing, reviewing, and editing of the final draft. My supervisors SM and RM assisted with the interpretation of results and writing, reviewing, and editing the final draft.

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Chapter 5: I solely wrote the final discussion chapter with edits and review conducted by my supervisors KH and NRC.

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List of Abbreviations

ABTC	Animal Bite Treatment Center
CDC	Centers for Disease Control and Prevention
CI	Confidence Intervals
CNS	Central nervous system
DOH	Department of Health
DFAT or DFA	Direct Fluorescent Antibody Test
DALY	Disability-Adjusted Life Year
ERIG	Equine Rabies Immunoglobulin
FAO	Food and Agriculture Organization of the United Nation
FETPAFI	Field Epidemiology Training Program Alumni Foundation
GARC	Global Alliance for Rabies Control
HDR	Human dog ratio
IBCM	Integrated Bite Case Management
ID	Intradermal(ly)
IM	Intramuscular(ly)
LFD	Lateral flow device
LGU	Local Governmental Unit
LMIC	Low- and middle-income country
MAO	Municipal Agriculture Office
MDV	Mass dog vaccination
MHO	Municipal Health Office
MRC	Medical Research Council
NaRIS	National Rabies Information System
NRPCP	National Rabies Prevention and Control Program
NTD	Neglected Tropical Disease
OIE	World Organisation for Animal Health
PCHRD	Philippine Council for Health Research and Development
PCR	Polymerase Chain Reaction
PEP	Post-Exposure Prophylaxis
PHO	Provincial Health Office
PrEP	Pre-Exposure Prophylaxis
PIDSR	Philippine Integrated Disease Surveillance and Response
RABV	Rabies virus
RADDL	Regional Animal Disease Diagnostic Laboratory
RDT	Rapid Diagnostic Test
RHU	Rural Health Unit
RIG	Rabies Immunoglobulin
RITM	Research Institute for Tropical Medicine
SPEEDIER	Surveillance integrating Phylogenetics and Epidemiology for Elimination of Disease: Evaluation of Rabies Control in the Philippines
UNEP	United Nations Environment Programme
WHO	World Health Organization
WOAH /OIE	World Organisation for Animal Health (founded as OIE)

CHAPTER 1

An introduction to rabies surveillance, control, and elimination

1.1 Neglected Tropical Diseases

The World Health Organization (WHO) recognizes a core group of twenty pathogens as neglected tropical diseases (NTDs) that are "*mainly prevalent in tropical areas, where they mostly affect impoverished communities and disproportionately affect women and children*" (WHO Second Report NTDs, 2013). This list includes infectious diseases with causative agents ranging from helminths (e.g. hookworms and roundworms) to protozoans (e.g. leishmaniasis and Chagas disease), to bacteria (e.g. leprosy), to viruses (e.g. rabies and dengue). While NTDs affect the health, social, and economic situation of more than one billion people living in low- and middle-income countries (LMICs), implementing and sustaining effective control measures is challenging due to the complex life cycles and transmission dynamics often involving animal reservoirs (WHO NTDs, 2023).

Characteristics commonly attributed to NTDS include: 1) they are ancient conditions that have plagued humans for centuries, 2) they have a high prevalence significantly underreported in epidemiological data, 3) they are strongly correlated to rural poverty, particularly in agricultural areas with subsistence farming, 4) they often persist as chronic ailments lasting years or even for a lifetime, leading to long-term disabilities, disfigurements, and stigmatization, which promote further poverty, and 5) they usually are associated with high disease burden but a low incidence of mortality (Hotez, 2022).

Yet, one NTD stands out as an anomaly to the latter shared features listed above—the rabies virus. While rabies is unquestionably an ancient disease affecting impoverished communities primarily in LMICs with a burden severely underreported, it also frequently infects people living in urban areas and is invariably fatal once symptoms appear. The Global Burden of Disease Study (GBD) estimates that each year 100,000 to 200,000 people die from NTDs (GBD, 2020), of which an estimated 59,000 are likely due to rabies (Hampson *et al.*, 2015). Moreover, unlike the vast majority of NTDs, rabies is essentially 100% vaccine-preventable in both humans and animals, increasing the feasibility of elimination and making strategies more straightforward (Hemachudha *et al.*, 2013; Zero by 30, 2018).

In 2012, WHO developed the first road map for the prevention and control of NTDs, resulting in tremendous progress in reducing the disease burden for 600 million people and 42 countries or territories eliminating at least one of the twenty core NTDs (WHO, 2020). This includes notable progress for dracunculiasis, nearing eradication (Hopkins *et al.*, 2021); lymphatic filariasis, with verified elimination from 15 countries (Davis *et al.*, 2019); trachoma, with 13 countries claiming elimination (West, 2020); and onchocerciasis, with verified elimination in 4 countries in the Americas (Lakwo *et al.*, 2020). Despite this impressive headway, most targets set to be achieved by 2020 were not met and a new road map was developed in line with Sustainable Development Goal 3.3 aiming to end NTDs by 2030 (UN SDG, 2021). For rabies, Mexico was the only country to reach targets set by the initial 2020 NTD road map and be validated as free of dog-mediated human rabies deaths by WHO in 2019 (Aréchiga, 2022).

1.2 Rabies Virus

The pathogen responsible for the disease rabies is a negative-sense single-stranded RNA virus (RABV) belonging to the genus Lyssavirus (Greek: lyssa meaning “rage”) and family Rhabdoviridae (Greek: rhabdos meaning “rod”) (Tordo & Poch, 1988; Fooks & Jackson, 2020). Similar to other viruses classified within this family, the RABV genome of approximately 12,000 nucleotides is organized helically within a host-derived lipid envelope which forms a distinctive rod or bullet-shaped morphology. The viral genomic information contains only five genes encoding structural nucleo- (N), phospho- (P), matrix (M), glycol- (G), and large- (L) proteins (Dale & Peters, 1981; Ogino *et al.*, 2016).

As a zoonotic disease, rabies is most often transmitted to humans via animal bites, inoculating infectious saliva into victims' subcutaneous tissue or muscles. Non-bite-related exposures from scratches, licks, or contact with infected saliva or brain tissue into open wounds or the mucosal membrane are also common, but less likely to result in RABV transmission (WHO TRS, 2018). While all mammals can be infected with and transmit rabies, prolonged circulation of the virus is primarily sustained in a few reservoir species of bats and carnivores, including domestic dogs (Velasco-Villa *et al.*, 2017). Each single reservoir host maintains one of several genetically distinct strains of RABV, with transient spillover events possible but rarely with successful adaptation or sustained transmission cycles in the new host species (Mollentze, Biek, & Streicker, 2014).

Following inoculation of RABV from an animal bite or exposure event, viral replication occurs in the muscle or other local tissues. As a highly neurotropic virus, RABV then spreads to motor axons in the peripheral nervous system, moving centripetally towards the central nervous system (CNS) at 5-100 mm per day (Ugolini *et al.*, 2008). Typically, virions reach the spinal cord first and then rapidly ascend towards the brain infecting the neurons, with centrifugal spread to the salivary glands (where the virus sheds in the saliva), skin, cornea, and other organs (Fooks & Jackson, 2020). Due to this pathogenic mechanism, the incubation period is highly variable depending on the RABV viral load (i.e. larger viral loads leading to shorter incubation periods), severity of exposure/proximity to the CNS, species of animal, RABV variant, and immune status/age of the host (Cleaveland *et al.*, 2002; Fooks & Jackson, 2020; Mesquita *et al.*, 2017). The average incubation period is between 20 to 90 days but can range from a few days to multiple years for symptoms to appear (Smith, Fishbein, Rupprecht, & Clark 1991). However, human rabies deaths reporting an incubation period longer than one year are rare, occurring in less than 3% of cases (Baer, Bellini, & Fishbein, 1990), with those reporting symptoms several years after exposure being disputed altogether (Iyengar, 1935; Gavrila, Iurasog, & Luca, 1967; Iwasaki *et al.*, 1985).

While the time span of the incubation period varies considerably in humans, the duration of the other clinical stages of disease (prodrome, acute neurological, coma, and death) is more predictable. The prodromal period begins when RABV enters the CNS, damaging tissue and causing the victim to become symptomatic. Once this happens, infected humans manifest non-specific symptoms (e.g. fever, chills, malaise, headache, insomnia, irritability, pain/paresthesia at the bite site, etc.) for 2-10 days (Hemachudha *et al.*, 2002). This is followed by a rapid deterioration in health with the sudden onset of neurological symptoms and encephalitis. There are two forms of the disease: encephalitic (~80% of patients), also known as "classic" or "furious" rabies, and paralytic rabies (~20% of patients) (Hankins & Rosekrans, 2004). The former is generally characterized by erratic behavior and outbursts of aggression, while the latter manifests as rapid muscle weakness. Both forms typically progress to coma, organ failure, and then death within 14 days of the onset of symptoms (Hemachudha *et al.*, 2013).

1.3 Burden of Rabies

Dog-mediated rabies is by far the greatest threat worldwide in terms of human rabies cases, causing an estimated 59,000 deaths [95% CIs: 25,000-159,200] annually (Hampson *et al.*, 2015). Rabid dogs are responsible for transmitting more than 99% of all human rabies cases globally, occurring primarily in LMICs in Asia (59.6%) and Africa (36.4%). In endemic countries, data spanning multiple sources consistently estimate a human rabies incidence ranging from 1.5 to 5 deaths per 100,000 persons per year, including a study discussed in this thesis (Chapter 4) using data from the Philippines. Despite a low R_0 between 1-2 and low endemicity in the dog population, rabies persists and remains the zoonotic disease with the highest case-fatality rate (Hampson *et al.*, 2009: Cleaveland *et al.*, 2014; Mancy *et al.*, 2022).

Asia has the highest burden of rabies and expenditure on PEP, with an estimated 35,172 human deaths (Hampson *et al.*, 2015), and costs upwards of USD 1.5 billion per year (Anderson & Shwiff, 2015). However, the Philippines has a relatively low burden for this region, reporting 200-300 deaths annually (Philippines DOH, 2018). With a human population of nearly 114 million (World Bank, 2021), this equates to a human rabies incidence of <0.27 per 100,000 persons per year, which is similar to estimates by Hampson *et al.* (2015) of between 0.038 and 0.19. While some provinces have a low endemicity or have been declared rabies-free (NRPCP Strategy, 2020), the low incidence of human cases in the Philippines can be largely attributed to immense government efforts to ensure accessibility of free PEP at >500 Animal Bite Treatment Centers (ABTCs) established widely throughout the country (Amparo *et al.*, 2018). Yet, consequently, the number of bite patients seeking PEP has increased almost sevenfold from the initiation of the free PEP policy in 2007 (~197 per 100,000 persons/year) compared to the last seven years (>1,030 per 100,000 persons/year), resulting in an unsustainable burden on the local and national health system budget (NRCPC Strategic Plan, 2020). Despite this major investment, the Philippines has been unable to eliminate dog-mediated human rabies deaths, which they are now aiming to achieve by 2030.

Over the last century, essentially all high-income countries have been able to achieve the elimination of dog rabies across Western Europe, North America, and parts of Asia, such as Japan and Taiwan. Additionally, a few LMICs in Latin America have recently demonstrated tremendous success using coordinated mass dog vaccination campaigns to reduce dog-mediated rabies by 98% across the region (Velasco-Villa *et al.*, 2017), with Mexico receiving WHO validation in 2019 for zero human cases transmitted by dogs (Aréchiga, 2022). These achievements seen in Latin America can be majorly attributed to substantial collaboration and coordination with the veterinary sector, including allocating 17% of funds to dog vaccination (compared to an average of <1.5% in other endemic countries) (Hampson *et al.*, 2015). Despite this progress, rabies continues to threaten the lives and livelihoods of millions of people in over 150 countries.

Rabies is a neglected disease of poverty. Much of the economic burden associated with rabies is placed on governments and individuals in resource-poor settings that cannot afford these costs. In a global burden study by Hampson *et al.* (2015), it was estimated that dog-mediated rabies has an economic cost of 8.6 billion USD [95% CIs: 2.9-21.5 billion) annually primarily due to premature deaths, expenditure on post-exposure prophylaxis (PEP), and loss of income. For individuals, high out-of-pocket costs for PEP can oftentimes be more than a month’s salary, imposing a major burden on livelihoods, especially in poor rural populations (Changalucha *et al.*, 2019). Furthermore, the loss of livestock from rabies threatens the food security of families who depend on them for subsistence. Other diseases resulting in higher mortality in the agriculture sector are typically prioritized over rabies for being viewed as having more economic importance (Cleaveland *et al.*, 2014). Lack of funding for adequate surveillance leads to severely underestimated cases, perpetuating the cycle of neglect that limits advocacy while rabies continues to spread amongst the world's most vulnerable populations.

1.4 Rabies Control and Elimination

In 1885, Louis Pasteur developed a human vaccine capable of preventing infection, and thus death, caused by the rabies virus (Rappuoli, 2014). Shortly after, in the early 1900s, animal rabies vaccines were developed with the first mass dog vaccinations taking place in the 1920s (Umeno, 1921). With near 100% effectiveness, the vaccination of humans and animals has been a cornerstone of rabies control programs aiming to stop preventable human deaths.

Mass dog vaccination (MDV) is consistently found to be the most cost-effective strategy for reducing the economic and human impacts from rabies and achieving elimination (Cleaveland *et al.*, 2003; Fitzpatrick *et al.*, 2014; Shwiff *et al.*, 2018). MDV is highly effective at interrupting rabies transmission in the reservoir population, reducing the incidence of rabid dogs and thus, the incidence of exposure and resulting human deaths (Abela-Ridder *et al.*, 2016; Lankester *et al.*, 2014). However, MDV campaigns must be delivered systematically, achieving over 70% coverage of the susceptible dog population homogeneously across a region to maintain adequate immunity in the dog population (Townsend, Sumantra *et al.*, 2013; Freuling *et al.*, 2013; Ferguson *et al.*, 2015). Moreover, annual or continuous MDV campaigns need to be sustained for 3-7 years, or even longer where re-emergence from wildlife rabies or bordering endemic areas is likely (Zinsstag *et al.*, 2017; WHO TRS, 2018). The majority of endemic LMICs face funding and implementation challenges, limiting the delivery of MDV at the scale and extent required for elimination (LeRoux *et al.*, 2018). Yet, recent studies have demonstrated that MDV can be successful even in resource-deprived settings, including Bhutan, Goa State in India, and Tanzania (Tenzin *et al.*, 2012; Gibson *et al.*, 2022; Hayes *et al.*, 2022).

While MDV alone is enough to eliminate rabies from the dog population, it must be done in parallel with PEP administration to people bitten by suspected rabid animals to prevent human deaths. However, PEP—which includes both human rabies vaccine and rabies immunoglobulin (RIG)—is expensive and the costs of indiscriminately provisioning PEP (i.e. without assessing for risk of exposure) are often unsustainable for most governments. Switching to the shortened 1-week intradermal (ID) PEP regimen recommended by WHO from more expensive intramuscular (IM) injections, saves costs ($20 USD vs. $100 USD), vaccine (<1 vial vs. 4 vials), and time (7 days vs. 14-28 days) (Bote, Nadal, & Abela, 2023). Furthermore, the WHO Rabies Modelling Consortium (2018) concluded that switching to the ID regimens is extremely cost-effective, estimating costs of $635 USD per death and $33 USD per disability-adjusted life year (DALYs) averted. However, even the shortened ID regimens can incur high costs if administered indiscriminately, as shown in Chapter 4 of this thesis. Estimates suggest that globally more than 29 million bite patients receive PEP each year at a cost of 1.7 billion USD in direct expenditure and an additional 1.31 billion USD in indirect costs (Hampson *et al.*, 2015). Accessibility and availability of PEP create major obstacles for those exposed to rabies, particularly in areas experiencing inequalities in access to healthcare (Changalucha *et al.*, 2019).

Navigating effective and appropriate (i.e. cost-effective) PEP policies entails a delicate balance. Countries improving access to free PEP provisioning to bite patients often face immense costs from spending on unnecessary PEP for bites from healthy animals (Amparo *et al.*, 2018). Moreover, once free PEP policies are introduced, demand and health-seeking behavior can remain high, even when the incidence of rabies in the dog population is reduced to near zero (Rysava *et al.*, 2019; Lechenne *et al.*, 2017; Rajeev *et al.*, 2019). However, this is not always the case, as seen in Pemba Island in Tanzania where health-seeking increased with free PEP policies and declined dramatically once rabies was controlled (Lushasi *et al.*, *expected 2023*). Some explanations for variation in PEP demand in a community once dog rabies is controlled are subsequent changes in availability/accessibility of PEP following control and local levels of trust in the government/health sector i.e. whether they believe rabies incidence is actually zero – both of which can influence health-seeking behavior. Alternatively, when PEP must be purchased by the individual, this leaves the most vulnerable populations unable to afford or access this life-saving vaccine. To find a middle ground between ensuring PEP accessibility to rabies exposures and not spending limited resources indiscriminately, enhanced surveillance assessing patients' risk of rabies is required (WHO Rabies Modelling Consortium, 2019).

In addition to dog and human vaccination, the third central pillar for rabies elimination strategies is strengthening surveillance (WHO TRS, 2018). Here, disease surveillance is defined using its four basic components as (1) continuous systematic collection, (2) analysis, interpretation, and (3) dissemination of information, feedback on outcome-specific data, or health events, (4) leading to a response (Davis *et al.*, 2000; Franka & Wallace, 2018). Historically and presently, rabies surveillance has been based on ineffective methods that do not accurately detect human or animal cases, such as only activating surveillance mechanisms retrospectively following a human death (Townsend *et al.*, 2013). Lack of robust and routine surveillance leads to underreporting of human and animal cases, concealing the true magnitude of devastation caused by rabies. This exacerbates the issue of insufficient funding for rabies control programs and the prioritization of diseases other than rabies, which leads to late detection of incursion events and slow response times to outbreaks. In the absence of effective surveillance, regions already declared rabies-free or close to elimination, can easily have all progress undone by an incursion that spreads undetected, as seen in the emergence of dog rabies in Bali, Indonesia in 2008 (Purwo Suseno *et al.*, 2019).

For strengthened surveillance, diagnostic testing is an important element to confirm animal cases. In endemic LMICs, laboratory capacity is normally limited in terms of infrastructure, equipment, and training. Also, severe constraints on sample submission due to challenges with collection, transport, and storage, bring about a deficiency of data for confirmation and genomic analysis (Brunker *et al.*, 2020). Typically, national guidance for animal testing in endemic countries is outdated, specifying a handful of sample submissions each year which is often done randomly and with opportunistic biases (Hampson *et al.*, 2016). New technological advances, such as lateral flow devices (LFDs) [Bionote: sensitivity of 0.95 and specificity of 1.00], have the potential to resolve some of these challenges by allowing a simple means for in-field testing (Kimitsuki *et al.*, 2020; Mananggit *et al.*, 2021). Yet, there are currently no official guidelines for the use of LFDs.

Given the low endemicity and difficulty of sample collection for confirmation, adequate rabies surveillance requires risk-based assessments and subsequent investigation/follow-up of suspect biting animals. This not only has the potential to increase the detection of animal cases but also to make more accurate PEP decisions. A study by Ma *et al.* (2020) showed high sensitivity and specificity of detection of persons exposed to rabies using only risk assessment data i.e. without confirmation diagnostic testing. This risk-based approach typically uses health clinics as sentinels for bite patients seeking care. However, with varying levels of health-seeking behavior amongst endemic LMICs, it can be challenging to find all exposed bite patients. In endgame settings aiming to verify rabies elimination, more time-intense contact tracing may even be necessary, though usually not an option due to limited capacity and resources (Lushasi *et al.*, *expected 2023*).

1.5 Rabies, One Health & Zero by 30

In 2018, the Tripartite [FAO, WOAH/OIE, & WHO] and the Global Alliance for Rabies Control (GARC) developed *Zero by 30: The Global Strategic Plan to end human deaths from dog-mediated rabies by 2030* (WHO, OIE, FAO, & GARC, 2018). The objectives of this strategy are: 1) to effectively use vaccines, medicines, tools, and technologies, 2) to generate, innovate and measure impact, and 3) to sustain commitment and resources. As one of the few zoonoses with an official elimination target set by international organizations, the *Zero by 30* goal reveals considerable dedication from the global community to eliminate dog-mediated rabies (Tidman *et al.*, 2022). Fundamental to this comprehensive framework is the concept of One Health, advocating for intersectoral collaboration and coordination from human and animal health sectors to achieve rabies freedom.

The concept of One Health is not new. In fact, the notion that the health of all living organisms is interconnected has been around in various forms throughout human history, going back to Hippocrates' "*On Airs, Waters and Places*" and Aristotle's concept of comparative medicine (Wear, 2018; Dunlop & Williams, 1996). To this day, the conceptualization of "One Health" is continuing to evolve, influencing levels of awareness, acceptance, adoption, and implementation strategies within the global health community (Gibbs, 2014). The increasing impact of threats linked to One Health (i.e. antimicrobial resistance, emerging infectious diseases, climate change, etc.) has revitalized the emphasis of this concept over the past decade. Recently, global policymakers have demonstrated their commitment to building One Health systems and capacity through the establishment of the One Health High-Level Expert Panel (OHHLEP) in May 2021, and the launch of the *One Health Joint Plan of Action* (FAO, UNEP, WHO, WOAH/OIE, 2022). An updated definition for One Health was issued by the OHHLEP, which has been adopted by the Quadripartite [FAO, UNEP, WHO, WOAH] (Adisasmito *et al.*, 2022):

> "*One Health is an integrated, unifying approach that aims to sustainably balance and optimize the health of humans, animals, plants, and ecosystems. It recognizes the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and interdependent. The approach mobilizes multiple sectors, disciplines, and communities at varying levels of society to work together to foster well-being and tackle threats to health and ecosystems while addressing the collective need for clean water, energy and air, safe and nutritious food, taking action on climate change, and contributing to sustainable development.*"

While the more conventional, older domain of One Health focuses on the interface between the health of humans, animals, plants, and the environment, the updated OHHLEP definition interprets One Health more comprehensively, focusing on the entire system that encompasses these sectors, including their interactions and the processes that influence dynamics within the system (Laing *et al.*, 2023). This broadened, more recent, definition integrates evolving attitudes and ways of thinking about One Health approaches by incorporating more disciplines (i.e. social sciences) and sectors (i.e. policy and economics) and considering variation in contextual factors between settings. Yet, while the expanded OHHLEP definition is imperative for delineating the evolution of practitioners' and researchers' understanding and competency in integrative system-level approaches, it has also added further challenges to the interpretation of One Health approaches and the streamlining of decision-making practices. To improve the capacity of a trained workforce capable of implementing One Health in action, the Network for Ecohealth and One Health (NEOH) has recommended updated core competencies for One Health that include both the older (interface-based) and newer (system-based) streams of thought.

Typically, rabies control programs fall into the more traditional anthropocentric One Health interpretation, with approaches focusing on avoiding disease at the interface of only two sectors through interventions led by veterinary and public health professionals. Given the repeatedly demonstrated effectiveness of these conventional two-sector strategies in reducing the burden of rabies—particularly those with strong involvement from the animal health side like in Latin America—the field of rabies may be slower to adopt the expanded OHHLEP definition into practice. Much of the success seen in the Americas can be attributed to a high level of engagement from the veterinary sector to deliver extensive coordinated dog vaccination, in combination with enhanced laboratory-based surveillance, and robust national strategies promoting support of both the human and animal sectors (Velasco-Villa *et al.*, 2017). In addition to strong collaboration between human and animal sectors, these effective strategies were also sustainable, resulting from decades of continuous government prioritization, allocation of resources, and human capacity dedicated to control efforts.

However, while progress in the Americas has been a remarkable accomplishment, delivery of such ambitious resource-intensive campaigns has not yet been prioritized in the majority of endemic LMICs in Asia and Africa. Moreover, maintaining the level of effectiveness seen in the Americas in other settings will likely be challenging due to competing priorities and barriers to sustainability. Hence, reaching *Zero by 30* elimination goals in these countries will presumably require a diverse array of adapted One Health interventions and strategies that utilize limited available resources to facilitate sustained progress on the ground (Fahrion *et al.*, 2017). To address implementation barriers in more complicated settings, some national strategies may benefit from the adoption of the broader OHHLEP system-based approach of One Health in action. Rabies surveillance strategies could benefit from restructuring to incorporate a systems-level approach, monitoring the processes that promote the emergence and transmission of rabies cases, rather than focusing only on searching for the presence or absence of disease in humans and animals (Haesler *et al.*, 2023).

As a zoonosis included in the *One Health Joint Plan of Action* framework, the Quadripartite and One Health community (i.e. NEOH) will likely play a key role in expanding and guiding rabies control initiatives using system-based approaches (FAO, UNEP, WHO, WOAH/OIE, 2022). Rabies is the epitome of a One Health approach, providing an invaluable model for the implementation of One Health in action (Cleaveland *et al.*, 2014). To be effective, rabies control programs require joint engagement from various government ministries i.e. health and veterinary and/or agriculture, public and private sectors, local stakeholders, and community members. Building the capacity of intersectoral networks and connections not only supports rabies control efforts but also can be used to address other threats to public health (FAO, UNEP, WHO, WOAH/OIE, 2022). Workforces trained to capture surveillance data, detect suspect animals, and respond to rabies at the field or community level can perform activities for control measures, not only for rabies but for other zoonotic diseases. By building upon and connecting existing networks using One Health approaches for the prevention of NTDs, limited resources can be shared to improve the efficiency and the likelihood of sustainability of these disease control programs (Cleaveland *et al.*, 2014; Tidman *et al.*, 2022).

1.6 Integrated Bite Case Management

In general, infectious disease surveillance systems aim to detect the absence or presence and distribution of a pathogen through routine, systematic collection, analysis, interpretation, and dissemination of epidemiological data to inform decision-making and guide prevention and control measures (Lee & Thacker, 2011; CDC, 2012; Franka & Wallace, 2018; WOAH, 2022). Effective surveillance provides practitioners, policymakers, and stakeholders with timely and useful information that can be used to set priorities to manage disease control programs and target evidence-based action (Nsubuga *et al.,*2006; Drewe *et al.*, 2015). Recent efforts have been made to integrate health surveillance, with the successful integration of these systems demonstrating the ability to enhance performance through improved sensitivity, timeliness of detection, data quality, and acceptability (George *et al.*, 2020). Despite these perceived benefits, implementation challenges associated with fidelity, uptake, and sustainability necessitate further research and applied practice to improve the effective integration and delivery of these systems (George *et al.*, 2022). In LMICs, human and animal disease surveillance are often siloed, sectoral and inefficient, with priority placed on detection of human diseases, despite growing recognition of animal health surveillance as a key tool in for prediction of public health risks and early indication of emerging zoonotic disease (Meidenbauer, 2017).

Using the most basic definition, One Health surveillance involves "*collaboration amongst at least two of the following sectors: animal, human, and environment*" (Bordier *et al.*, 2020). Integrated Bite Case Management (IBCM) is a prime example of One Health surveillance, specifying cooperation between human and animal health sectors to conduct all four basic elements of surveillance: collection, analysis, dissemination, and response (FAO, UNEP, & WHO, 2022). IBCM is broadly based on the premise that the most efficient way to detect rabid animals and high-risk exposures that require PEP is by assessing the risk of rabies for bite patients using information about the health status of the biting animal. Implementation of the IBCM approach varies between settings in terms of operation and protocols, but all programs share the same fundamental components. These include six key activities: 1) reporting bite events, 2) performing risk assessments, 3) triggering animal investigations, 4) conducting animal investigations, 5) observing animal for 10-14 days (healthy animals) or collecting samples for dead/euthanized animals, and 6) sharing feedback and results across all involved sectors (Swedberg *et al.*, 2022).

In terms of the four elements of surveillance, IBCM prescribes the following actions to be conducted: 1) Collection: Risk-based assessment data are collected for each bite patient using information about the health/history of the biting animal. Animal investigation data (e.g. health/vaccination status, signs/symptoms of rabies, and diagnostic laboratory test results) are collected by the animal health sector for any animal deemed suspicious. 2) Analysis: Practitioners, typically human health workers or epidemiologists, analyze risk assessment data to determine the incidence of rabies exposure and subsequent PEP provisioning, and identify high-risk areas. Epidemiologists or animal health workers analyze the animal investigation data, assigning the WHO case definition ("not a case", "suspected", "probable" or "confirmed") (WHO TRS, 2018) and estimating the incidence and distribution of animal rabies cases. 3) Dissemination: The human health sector reports high-risk exposure events to the animal health sector, and then the animal health sector reports back the results of the animal investigation. Epidemiologists share analysis of the data with all relevant sectors and stakeholders. 4) Response: The human health sector uses animal investigation data to make PEP decisions and determine if more in-depth contact tracing is necessary. If a rabid animal is detected, the animal health sector investigates the surrounding area in search of other potential human or animal exposure events. Ideally, the interpretation of the collated data on the incidence of rabies exposures and animal rabies cases is used to implement prevention and control measures, like MDV, to target high-risk areas.

While protocols similar to IBCM have been implemented in high-income settings in various forms over the last century (e.g. Canada, the United States, and Western Europe), the intervention now rebranded as "IBCM" has been specifically adapted and promoted for use in LMICs with endemic dog rabies. Over the last decade, IBCM pilot studies and programs have been implemented sub-nationally in a range of countries including Cambodia, Chad, Cote d'Ivoire, Guatemala, Haiti, India, Indonesia, Kenya, Madagascar, Malawi, Mozambique, the Philippines, Peru, Tanzania, and Vietnam (Lechenne *et al.*, 2017; Wallace *et al.*, 2015; Rajeev *et al.*, 2019; Lushasi *et al.*, 2020; Gibson *et al.*, 2022). Many of these programs were/are implemented with the purpose of integrating enhanced routine surveillance into national policy. However, earlier initiatives to establish this approach i.e. in Haiti and Bali, Indonesia (between 2010-2013), initially used IBCM as a tool for emergency management to control emerging rabies outbreaks (FAO, 2013; Wallace *et al.*, 2015), then later utilized IBCM protocols as a routine surveillance method.

In the *Zero by 30* strategy and the WHO expert consultation on rabies, international organizations have promoted the use of IBCM as a gold standard, cost-effective method to enhance rabies surveillance and improve data quality (Zero by 30, 2018; WHO, 2018). However, there currently is limited guidance on how to operationalize IBCM and how strategies could vary between different settings. While there has been evidence of effective use of IBCM (e.g. Haiti, Tanzania), many programs are in the beginning phases of implementation and have not yet synthesized lessons learned. Similar to other key rabies control interventions (i.e. MDV campaigns, PEP administration), it is likely that rabies-endemic countries will struggle to initiate this call to action without guidelines and support from experts in the field. Crucial to successful implementation, local stakeholders need to understand the value of IBCM, how IBCM activities lead to desired outputs and outcomes, how to implement IBCM effectively and sustainably, and be able to connect these lessons to the overall aim of rabies elimination.

Of the countries where IBCM has already been established, some valuable lessons learned have emerged, particularly in Haiti, one of the longest-established programs and an important exemplar of IBCM. Findings from an initial pilot study in Haiti (2013-2015) demonstrated that IBCM increased reporting of rabid animals 18-fold compared to prior years; ruled out rabies, and thus PEP and subsequent costs, for >60% of bite patients where an animal investigation was conducted; improved patient health outcomes; and reduced the cost per death averted, making IBCM more cost-effective than no IBCM (Wallace *et al.*, 2015; Undurraga *et al.*, 2017). Furthermore, IBCM enhanced the detection of human exposures and animal cases and improved communication between human and animal health in additional settings like Tanzania, Chad, and the Philippines (Lushasi *et al.*, 2020; Lechenne *et al.*, 2017; Mbaipago *et al.*, 2020; Rysava *et al.*, 2019). In Chad, the Philippines, and Madagascar, risk assessment data from IBCM showed potential as an effective tool for estimating the burden of rabies and providing means for more judicious administration (Madjadinan *et al.*, 2020; Rysava *et al.*, 2022; Rajeev *et al.*, 2019).

With the goal to end human deaths from dog-mediated rabies by 2030, expansion of the implementation and funding for IBCM programs is likely to continue as a key element of national rabies elimination strategies. However, as a novel intervention, there are still many unanswered questions and lessons to be learned about how to sustainably implement IBCM cost-effectively. Because contextual features are vastly different amongst endemic LMICs (e.g. health system structure, financial resources, health/animal sector capacity, PEP-seeking behaviors, etc.), it is to be expected that there will be variation in implementation strategies between these settings. Where one country might experience challenges, another could experience opportunities for success. Therefore, further research is required to assess the feasibility of delivering IBCM in a variety of contexts and its potential to be scaled up for integration into national strategies, as discussed in Chapter 3 of this thesis.

1.7 Implementation Research

Like the concept of One Health and the approach IBCM, the field of implementation research (or science) has been gaining recognition over the last decade for its importance in global health, but there remains some level of perplexity about its definition and scope (Remme *et al.*, 2010; Bauer *et al.*, 2015). To better understand the definition of implementation research, is it critical to first be able to differentiate between the term *efficacy*, defined as "*the performance of an intervention under ideal and controlled circumstances*", and *effectiveness*, defined as the intervention's "*performance under 'real-world' conditions*" (Singal, Higgins, & Waljee, 2014). For this thesis, I will use the definition given by Allotey *et al.* (2008), which describes implementation research as:

> *"Applied research that aims to develop the critical evidence base that informs the effective, sustained, and embedded adoption of interventions by health systems and communities. It deals with the knowledge gap between*

> *efficacy, effectiveness, and current practice to produce the greatest gains in disease control.”*

When implementing interventions for disease control in LMICs, implementation research is a critical but often disregarded step that identifies how to implement interventions in a way in which they can be adopted by the community, practitioners, stakeholders, and the system (Allotey *et al.*, 2008; Bardosh, 2018). Many promising and effective interventions are known and available for the prevention and control of NTDs. Yet, real-world implementation of these interventions in resource poor LMICs can be complicated and nuanced, particularly when striving for sustainability (Bardosh, 2018; Hailemariam *et al.*, 2019). Multiple studies have been conducted generating evidence of the benefits and usefulness of conducting feasibility studies for One Health interventions tackling disease control, including for antimicrobial resistance in hospitals in Vietnam (Huong *et al.* 2021), elimination of schistosomiasis in Egypt (Ramzy *et al.*, 2020), and control strategies for brucellosis in India (Dhand *et al.*, 2021).

While *Zero by 30* advocates the need for further research assessing the feasibility of delivery, impact, and the potential for scale-up of IBCM programs, very few studies have been conducted/published on this topic so far. A recent publication by Schrodt *et al.* (2023) may be one of the first papers evaluating the feasibility of implementing IBCM using an electronic app to collect data in the long-established Haiti IBCM program. Findings from this study reveal that electronic app-based IBCM was more cost-effective than paper-based IBCM (a cost per death averted of $1,247 USD vs. $2,692 USD); prevented more human deaths annually (55 vs. 20); had a higher percentage of case outcomes correctly classified (100% vs. 94.5%); and was the preferred method of IBCM data collection amongst 100% of participants surveyed. Studies like this generate valuable evidence for lessons learned to improve the effectiveness of IBCM delivery, which can then be applied to new or existing IBCM programs in different settings. The more these lessons are shared between practitioners/stakeholders, the quicker IBCM protocols can be streamlined to reduce the waste of resources.

As a complex intervention (Hawe, 2015), IBCM has multiple components interacting between several stakeholders/sectors which aim to achieve numerous variable outcomes. To further add to this complexity, it can be difficult to change routine behaviors amongst bite patients, human and animal health workers, and government ministries, particularly without national support for new IBCM protocols. While there is flexibility within the degree to which IBCM can be adapted to the local context, the lack of guidance on how to tailor IBCM programs can limit success or waste time and resources (Craig *et al.*, 2018). To monitor program activities, outputs, and outcomes to allow evaluation of effectiveness and adaptations required during the program (i.e. as opposed to retrospectively), tools such as a Theory of Change (ToC) or process evaluations might be valuable when developed prior to implementation (Rogers, 2013).

Process Evaluations were first mentioned in 2008 MRC guidance (Craig *et al.*, 2008) as useful tools that "*can be used to assess fidelity and quality of implementation, clarify causal mechanisms and identify contextual factors associated with variation in outcomes.*" However, it was only in the last decade that guidance from the Medical Research Council (MRC) was developed (Moore *et al.*, 2015). This MRC process evaluation framework is valuable for interventions such as IBCM by helping to understand assumptions of why IBCM leads to desired outcomes (i.e. via a ToC) and evaluate how IBCM works in practice. Building this evidence base is vital to synthesize lessons learned for scale-up, to inform policy, and to adapt practices to optimize efficacy (Moore *et al.*, 2021).

1.8 Decision Tree Models

Poor quality epidemiological data leaves major gaps in the understanding of local rabies transmission dynamics, limiting the ability to develop effective policy and control strategies. Surveillance data plays a key role not only in designing and implementing rabies interventions but also in monitoring/evaluating their progress to measure fidelity and guide adjustments required to meet program objectives. This uncertainty of rabies epidemiology data and parameters can potentially hinder the success of control and elimination programs through a lack of valuable feedback to guide implementation and measure impact. Analytical tools, such as disease models, are invaluable for providing insights into the biological and human behavior mechanisms driving rabies transmission within the human, domestic dog, and wildlife populations. To account for this incomplete reporting, modeling methods can be used to estimate epidemiological data and probabilities within transmission dynamics more accurately.

Decision tree frameworks are an example of a simple probabilistic model that can be used to make quantitative predictions for values, such as the burden of rabies and costs associated with control programs. This type of method has been used in several studies aiming to estimate the magnitude of underreporting, particularly to measure global moralities due to rabies. In 2002, Cleaveland *et al.* used a decision tree model and field data from Tanzania to predict the likelihood of developing rabies after being bitten by a rabid animal based on factors such as bite location, severity, and PEP administered. Furthermore, in 2015 Hampson *et al.* adapted this approach to estimate the global burden due to rabies in terms of human deaths (~59,000), DALYs (>3.7 million), and economic costs (~8.6 billion USD). These methods have also been used to estimate epidemiological and economic data for 67 endemic LMICs (WHO Rabies Modelling Consortium, 2018), the burden of rabies and PEP costs in Madagascar (Rajeev *et al.*, 2019), and rabies incidence, biting behavior of rabid dogs, and health-seeking in Tanzania (Hampson *et al.*, 2016).

1.9 Thesis Preamble

In the following chapters of this thesis, I examine the implementation of rabies surveillance and control programs, particularly focusing on the One Health approach IBCM. Chapter 2 provides a broad overview of IBCM implementation in different settings across Africa, Asia, and the Americas, by interviewing practitioners and researchers with experience designing, implementing and/or managing these programs. Through thematic analyses, I aimed to understand how IBCM is conceptualized by experts in the field and compare/contrast how operationalization and barriers and facilitators to implementation vary across contexts. This chapter concludes that IBCM is not a one-size-fits-all approach and demonstrates the importance of adapting IBCM to the local context to achieve sustainable outcomes. For Chapter 3, I dove deeper into the development and effective delivery of IBCM implementation using a case study in the province of Oriental Mindoro, Philippines. Through a mixed methods process evaluation, I assessed: 1) the feasibility of effective delivery, 2) the extent to which IBCM was implemented as initially intended, and 3) how initial protocols adapted over the course of the study to fit the local context. Findings from this chapter showed that while IBCM was initially not feasible, adaptations made to the protocols during the study improved the effective delivery of IBCM, providing valuable lessons for adapting and scaling up guidance for expansion in the Philippines. In Chapter 4, I demonstrated the quantitative benefits of enhanced IBCM surveillance data as a tool to estimate the epidemiological and economic burden of rabies more accurately. Here, I used risk assessment data collected through IBCM in Oriental Mindoro province and input it into an adapted probabilistic decision tree model estimating the number of rabid dogs, total exposures, human deaths, and deaths/DALYs averted by PEP, and cost per death/DALY averted. The results highlighted that current PEP practices in the Philippines are inefficient without concurrent risk-based assessments to determine PEP administration decisions. Overall, the chapters in this thesis generate further evidence of the value of integrating One Health approaches into national rabies programs in LMICs to achieve elimination. In the final chapter, I conclude with a general discussion of key learnings from this thesis and summarize how they can be applied to rabies control strategies moving forward towards the *Zero by 30* goals.

CHAPTER 2

Implementing a One Health approach to rabies surveillance: Lessons from Integrated Bite Case Management

2.1 Abstract

As part of the '*Zero by 30*' strategy to end human deaths from dog-mediated rabies by 2030, international organizations recommend a One Health framework that includes Integrated Bite Case Management (IBCM). However, little is understood about the implementation of IBCM in practice. This study aims to understand how IBCM is conceptualized, exploring how IBCM has been operationalized in different contexts, as well as barriers and facilitators to implementation. Semi-structured interviews were conducted with seventeen practitioners and researchers with international, national, and local expertise across Africa, Asia, and the Americas. Thematic analysis was undertaken using both inductive and deductive approaches. Four main themes were identified: 1) stakeholders' and practitioners' conceptualization of IBCM and its role in rabies elimination; 2) variation in how IBCM operates across different contexts; 3) barriers and facilitators of IBCM implementation in relation to risk assessment, PEP provisioning, animal investigation, One Health collaboration, and data reporting; and 4) the impact of the COVID-19 pandemic on IBCM programs. This study highlights the diversity within experts' conceptualization of IBCM, and its operationalization. The range of perspectives revealed that there are different ways of organizing IBCM within health systems and it is not a one-size-fits-all approach. The issue of sustainability remains the greatest challenge to implementation. Contextual features of each location influenced the delivery and the potential impact of IBCM. Programs spanned from highly endemic settings with limited access to PEP charged to the patient, to low endemicity settings with a large patient load associated with free PEP policies and sensitization. In practice, IBCM was tailored to meet the demands of the local context and level of rabies control. Thus, experts' experiences did not necessarily translate across contexts, affecting perceptions about the function, motivation for,

and implementation of IBCM. To design and implement future and current programs, guidance should be provided for health workers receiving patients on assessing the history and signs of rabies in the biting animal. The study findings provide insights in relation to the implementation of IBCM and how it can support programs aiming to reach the *Zero by 30* goal.

2.2 Introduction

Effective rabies vaccines for humans and animals have been available for over a century, providing means to eliminate this fatal and incurable zoonotic disease (Cleaveland & Hampson, 2017). Through mass dog vaccinations starting in the 1920s, rabies has been successfully eliminated from domestic dog populations in all high-income countries across Western Europe, North America, and parts of Asia, such as Japan and Taiwan (Hampson *et al.*, 2009; WHO TRS, 2018). In addition, several low- and middle-income countries (LMICs) in Latin America have demonstrated success in reducing dog-mediated rabies cases by over 98% through large-scale coordinated dog vaccination programs (Wallace, Etheart *et al.*, 2017; Velasco-Villa *et al.*, 2017). Despite this significant progress, an estimated 59,000 people still die from dog-mediated rabies every year, with the vast majority in resource-poor countries in Africa and Asia (WHO TRS, 2018; Hampson *et al.*, 2015).

There are several challenges that LMICs encounter while attempting to reduce the burden of rabies within their populations. First, to control and eliminate rabies a high vaccination coverage, on the order of at least 70% of the susceptible dog population, must be sustained for 3-7 years via recurrent annual vaccination campaigns (WHO TRS, 2018). Yet many LMICs have not initiated routine dog vaccination (Wallace, Undurraga *et al.*, 2017). Furthermore, countries face the threat of reintroductions if endemic rabies circulates at their borders (Undurraga *et al.*, 2017). Second, post-exposure prophylaxis (PEP)—which is needed immediately after a bite from a rabid dog to prevent the fatal onset of rabies—is often expensive for both bite victims and governments. As a result, PEP availability is frequently limited, especially in rural areas (Changalucha *et al.*, 2019; Lechenne *et al.*, 2017). The costs incurred by PEP can even drain the finite budget available for rabies, without reducing rabies in the dog populations that are the source of exposures (Lavan *et al.*, 2017; Rysava *et al.*, 2019). Third, surveillance in LMICs is typically weak and does not capture accurate data on either human or animal rabies cases (Lushasi *et al.*, 2020). This significant under-reporting leads to a lack of awareness and understanding of the burden of rabies, which further results in limited community/stakeholder engagement and inadequate funding. Thus, the absence of robust surveillance gives rise to a cycle of underestimating the disease burden and consequently neglecting control measures, such as dog vaccination and PEP provisioning (Rysava *et al.*, 2019; Wallace *et al.*, 2015).

To overcome these challenges, the Tripartite [World Health Organization (WHO), World Organisation for Animal Health (OIE, now WOAH), Food and Agriculture Organization (FAO)] along with the Global Alliance for Rabies Control (GARC) developed the '*Zero by 30*' global strategic plan to end human deaths from dog-mediated rabies by 2030. Within this strategy, international organizations jointly recommend using a One Health framework that recognizes that the health of humans, animals, and their shared environment are interconnected (Lavan *et al.*, 2017). In order to control and eliminate rabies, the strategy advocates Integrated Bite Case Management (IBCM) (Zero by 30, 2018). WHO describes IBCM as an advanced surveillance method which "*involves conducting investigations of suspected rabid animals and sharing information with both animal and human health investigators for appropriate risk assessments*" (WHO TRS, 2018). Through multisectoral collaboration and communication, this One Health approach aims to enhance surveillance by increasing the detection of animal rabies cases and human exposures to rabies, as well as to improve PEP allocation and compliance (Wallace, Etheart *et al.*, 2017; Lushasi *et al.*, 2020; Etheart *et al.*, 2017).

While the objectives, aims, and benefits of IBCM are becoming better known by international organizations and experts in the field, this approach is still relatively new and has only been implemented within the last decade. Moreover, official guidelines for IBCM and risk assessments in relation to the biting animal were only first mentioned in 2018 in the WHO Expert Consultation on Rabies: Third report (WHO TRS, 2018). Peer-reviewed empirical evidence about the impact or implementation of IBCM remains weak. A PubMed search using keywords “novel surveillance” OR “integrated bite case management” AND “rabies” identified only eleven studies from four countries: Chad (Lechenne *et al.*, 2017; Mbaipago *et al.*, 2020), Haiti (Wallace, Etheart *et al.*, 2017; Wallace *et al.*, 2015; Etheart *et al.*, 2017; Undurraga *et al.*, 2017; Medley *et al.*, 2017; Ma *et al.*, 2020), the Philippines (Rysava *et al.*, 2019; Lapiz *et al.*, 2012), and Tanzania (Lushasi *et al.*, 2020). Although several IBCM programs have been implemented within the last decade, the approaches undertaken, and the lessons learned from these programs have not yet been synthesized. This study aims to understand how IBCM is conceptualized and practiced by stakeholders involved in rabies prevention and control programs around the world and the barriers and facilitators to its implementation.

2.3 Methods

This qualitative study was conducted among experts in the rabies field who have experience designing, implementing, and/or managing IBCM programs in a variety of epidemiological and geographical contexts (**Table 2.1**, *Appendix 1*). Purposive sampling of known professional networks was used to identify and recruit experts. All participants were contacted by email and provided with a participant information sheet outlining study objectives. Before the interview, participants were required to sign an informed consent, which assured their anonymity and asked permission to audio-record their interview. All interviews were conducted in English.

A total of seventeen participants with expertise on the topic of IBCM were interviewed including five international-level, six national-level, and six local-level experts. The majority of these participants had a degree in veterinary medicine (twelve); a doctoral research degree (nine); or both (five); and one had an MSc in medical statistics. All participants had some level of educational/experiential background in epidemiology. Their work experience ranged from academic, government, non-profit, and international organizations, with most having experience with more than one. Fourteen IBCM programs were included in the study representing thirteen countries in the Americas, Africa, and Asia. All IBCM programs were/are being implemented in countries with endemic dog rabies, with the exception of Rio Grande Do Sul, a state in Brazil which has not reported a dog or human rabies case since the 1980s.

Semi-structured one-to-one interviews (40-65 minutes) were conducted between January 2020 and August 2021. One interview was conducted face-to-face before COVID-19 restrictions prevented this interview method. The other sixteen were conducted over the videoconferencing platform, Zoom (Zoom Video Communications Inc., 2016). Interview topic guides were generated for each level of expertise: international, national, and local. The questions were designed to be open-ended and encourage experts to share their personal experiences and elaborate on the issues they felt to be most important. Each interview was audio-recorded, transcribed verbatim, pseudonymized, and then uploaded into NVivo 12 Pro software (QRS International Pty Ltd., 2018).

Data analysis was conducted by the PhD candidate and supervised by their secondary supervisor, an experienced qualitative researcher. The data was analyzed using a six-step thematic analysis as described by Braun and Clarke (Braun & Clarke, 2006). All transcripts were read for familiarization to develop initial codes. An inductive approach was used to develop descriptive codes identified from similar patterns, topics, and elements of the intervention, which were then collated into themes, categories, and subcategories (**Table 2.2**, *Appendix 2*). Transcripts were also coded deductively using assumptions underlying a logic model of IBCM, depicting the relationship between program activities and the intended impact of IBCM. Themes were developed and reviewed iteratively and checked for consistency and appropriateness, amending where necessary. Themes included: inputs, activities, outputs, outcomes, and aims. The transcripts were then compared for differences and similarities in how IBCM was operationalized, barriers and facilitators encountered during implementation, and the desired outcomes and aims of each IBCM program. Interviewees were sent a copy of the manuscript to validate accurate representation of their IBCM program. Their feedback was incorporated into the results and tables, which were created after all interviews were conducted.

Ethics Statement

This study involved human participants and therefore was reviewed and approved by the College of Medical, Veterinary & Life Sciences Ethics Committee at the University of Glasgow (Ref No. 200190081). All participants provided their written informed consent to participate in this study.

2.4 Results

2.4.1 Conceptualization of IBCM

Description of IBCM

Several experts first heard the term ‘Integrated Bite Case Management’ in relation to rabies control in Bali, Indonesia in 2011 (FAO, 2013). However, most learned of IBCM from a program in Haiti (Wallace *et al.*, 2015) or through their own experience. All programs used the term IBCM, except for three where their intervention was referred to as either a ‘One Health approach to bite management’ (Chad) (Lechenne *et al.*, 2017); ‘clinic-based surveillance’ (Madagascar) (Rajeev *et al.*, 2019); or a ‘One Health approach’ to guide PEP recommendations (Brazil) (Benavides *et al*. 201.

Experts described IBCM in a way that combined its key components (activities) with the role it plays (outputs/outcomes):

> *“IBCM at its simplest is the ability to provide a proper risk assessment, usually in the context of the exposing animal, in a way in which the outcomes of the risk assessment can impact the human treatment decision.”* (Expert #1, International level)

These components (activities) reported by experts were mostly consistent and aligned with the official WHO definition of an IBCM program. They included: 1) reporting a bite or exposure event, 2) performing a risk assessment, 3) triggering an investigation for any bite deemed high-risk, 4) conducting an animal investigation, 5) observing the animal for 10-14 days (to confirm a healthy animal) or collecting samples and testing for rabies (from dead/euthanized animals), and 6) sharing feedback and investigation results across sectors (**Figure 2.1**).

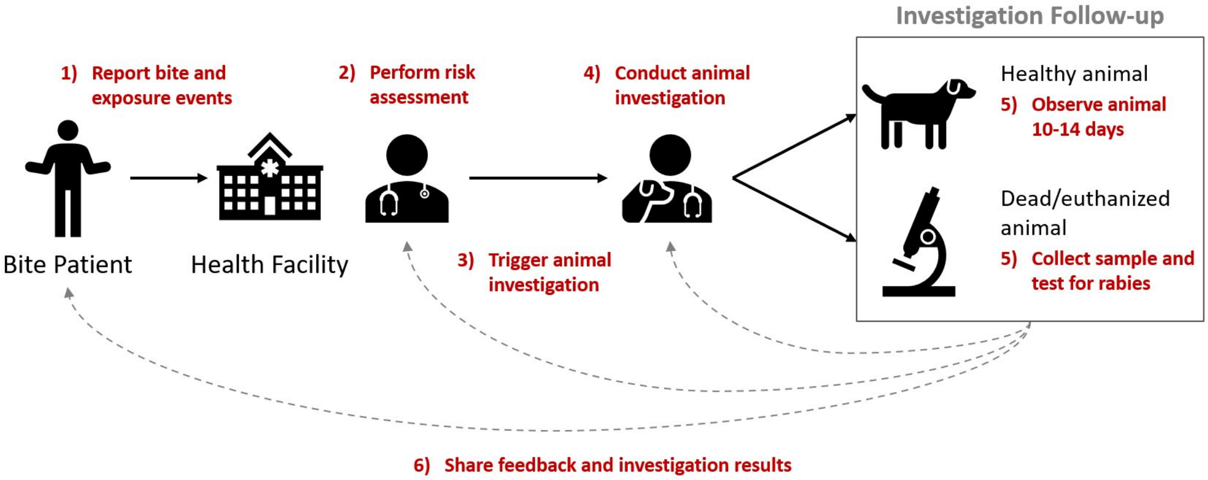


FIGURE 2.1 - KEY COMPONENTS OF IBCM. Annotated in red are the six components (activities) that comprise the IBCM approach with arrows and numbering indicating the sequential order of these components.

Although a consensus emerged about the required components of IBCM, there was still some uncertainty about the definition. Specifically, experts had varied opinions about whether IBCM must always be initiated by a bite event or determine treatment decisions or be used to specifically enhance surveillance. Therefore, while most interviewees perceived their work as being IBCM or similar to IBCM, some did not consider their program to formally be IBCM (for example, in Southern Brazil where the objective was not to strengthen surveillance but to better manage PEP).

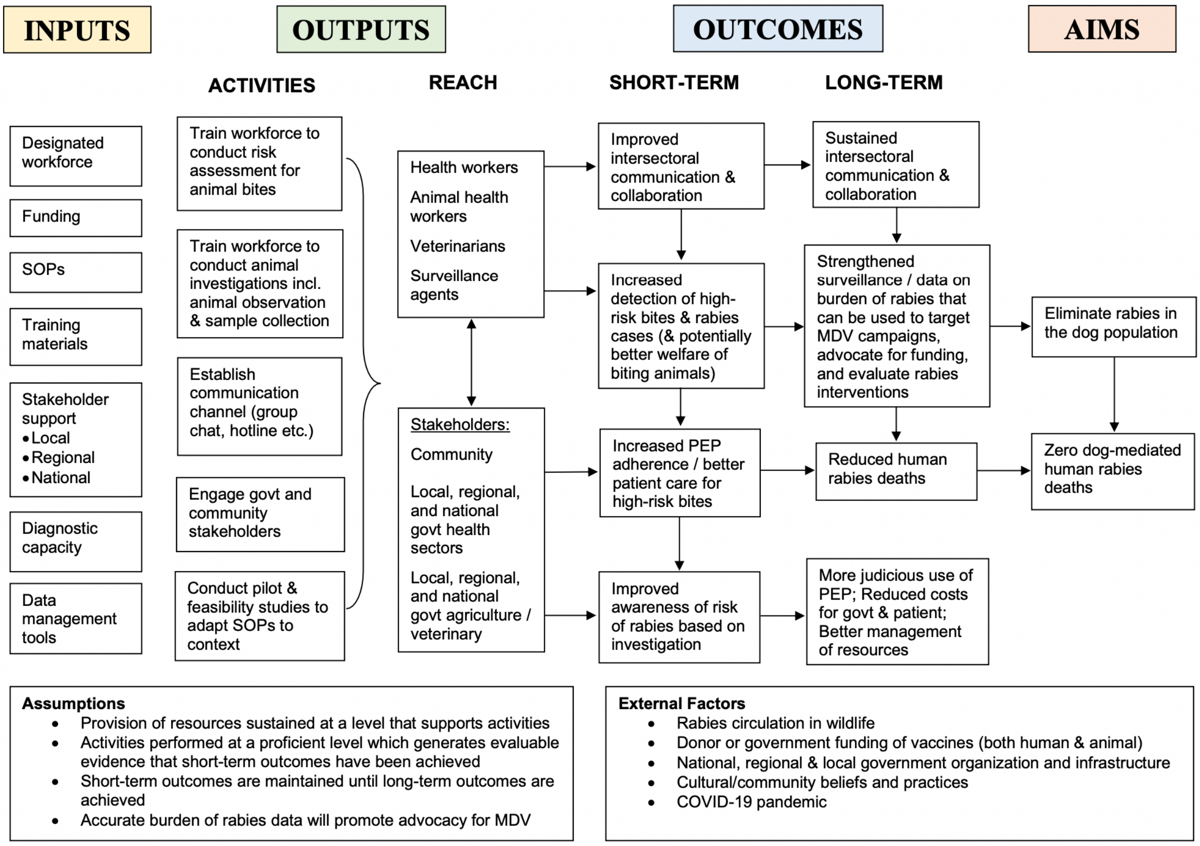
Participants' concept of IBCM evolved over time and with experience. Most international-level experts viewed this approach as “passive public health surveillance” initiated by any suspect rabid animal - not only from bites:

> *“I used to think it was integrated BITE case management. Whereas my attitude now is it’s the full investigation of a suspect animal, whether it’s for a bite or just a dog in the community behaving strangely.”* (Expert #3, International level)

Purpose of IBCM

Participants consistently identified several key roles of IBCM (outlined in the outcomes section of our conceptualized logic model, **Figure 2.2**). These roles were emphasized differently for each program and not all roles were relevant for every program. These roles were to a) enhance surveillance through improved case detection, thereby enabling evaluation of control and prevention measures; b) directly and formally connect the health sector to the veterinary sector; c) inform PEP administration, aiming to improve patient care and increase adherence; d) better manage limited resources through judicious use of PEP; and e) advocate for community/stakeholder support and funding for rabies programs.

> *"First, we're able to provide the best possible treatment for people who are bitten... Second, we're using less vaccines for humans, which is in short supply. Third, on the animal side, we're able to get much better intelligence on the circulation of the disease. And fourth, it helps move our control program forward... to target vaccination in areas where vaccination coverage was insufficient to prevent transmission."* (Expert #17, International level)



Assumptions

- Provision of resources sustained at a level that supports activities
- Activities performed at a proficient level which generates evaluable evidence that short-term outcomes have been achieved
- Short-term outcomes are maintained until long-term outcomes are achieved
- Accurate burden of rabies data will promote advocacy for MDV

External Factors

- Rabies circulation in wildlife
- Donor or government funding of vaccines (both human & animal)
- National, regional & local government organization and infrastructure
- Cultural/community beliefs and practices
- COVID-19 pandemic

FIGURE 2.2 - LOGIC MODEL OF IBCM. Representation of the relationship between resources (inputs), activities, outputs, short- and long-term outcomes, and aims of an IBCM program.

Experts agreed that countries with endemic dog rabies should all have a surveillance program, but opinions differed on when IBCM should be incorporated. A few experts viewed IBCM as an advanced surveillance strategy specifically meant for countries with a well-established control program that were close to elimination. Others argued that IBCM is important and required at all stages (e.g., endemic, emerging, elimination and post-elimination), as a part of routine surveillance:

> *"IBCM is needed as a country scales up its rabies elimination efforts and as an early intervention to try to bring down human deaths. It's needed in countries where 1) you have a lot of human deaths and you need to do a better job getting PEP to the people at risk and 2) as you really start to take elimination seriously, it's needed as a foundational system for evaluating the efforts that are going into vaccinating dogs. Then it's important in the endgame, post-elimination phase to continue to evaluate the risk to people bitten."* (Expert #3, International level)

2.4.2 Operationalization of IBCM

There was considerable variation in how IBCM was operationalized across settings, which were diverse in terms of their economic and epidemiological contexts, as described in **Table 2.1** (*Appendix 1*).

The most important prerequisites considered necessary for IBCM were the identification of a designated person/team responsible for investigating animals and health facilities (hospitals, clinics, etc.) where bites are reported, and PEP is administered. Several experts further mentioned the importance of stakeholder and community engagement prior to implementation.

The inputs and activities of each program are compared in **Table 2.3** (*Appendix 3*). The key input that differed between programs was who was identified and trained to carry out activities. Three categories of workforce were identified: fully hired, a combination of hired and local government, and fully local government. Other inputs that varied were the use of mobile applications for reporting/data management and the use of rapid diagnostic tests (RDTs) for in-field testing of samples.

Program activities were similar amongst each workforce category. IBCM programs with a fully hired workforce—meaning their primary job responsibility was rabies/IBCM and their salary was paid by external funding—relied on the same team or person to conduct most or all the IBCM components:

> *"We have trained surveillance agents... They all have the app on a tablet and go to the sentinel hospitals in their area weekly to check for bites... also through word of mouth. Then they go out and investigate the dog bites and report them."* (Expert #10, National level)

In contrast, programs with a fully local government workforce trained existing capacity to complete IBCM activities. This involved health workers (nurses, doctors, etc.) conducting risk assessments and alerting their animal health counterparts (animal health workers, veterinarians, etc.) to investigate biting animals. Programs with a combined workforce trained a hired team to conduct either the risk assessment or animal investigation, while the local government staff—or possibly volunteer medical/veterinary students—conducted the other.

Almost all IBCM programs used paper-based or electronic registers from health facilities to collect bite data. These were typically from district and regional-level hospitals supplying PEP but in some countries from rural community-level clinics with PEP access (e.g., Philippines). In addition to registers from health facilities, some programs used hotlines and/or trained local community health workers to report bite events. This was done particularly to enhance surveillance in rural areas with low PEP-seeking behaviors or limited access to PEP.

The mechanism to trigger animal investigations varied slightly from calling/ messaging the investigators, using hotline staff to notify them, and/or using group chats or submitting data into mobile apps that send notifications to investigators.

2.4.3 Barriers and Facilitators to IBCM Implementation

Barriers and facilitators reported by experts could be placed under five main categories. These consisted of risk assessment; PEP provisioning; animal investigation; the use of IBCM to facilitate One Health collaboration; and data reporting and mobile technology (**Table 2.4**, *Appendix 4*).

Risk Assessment

Findings from interviews indicated that IBCM programs with a hired workforce designated to perform risk assessments generally experienced fewer challenges than those with a local government workforce. Health workers were often stretched by busy workloads and responsibilities/priorities beyond rabies. Some commonly reported barriers were the high volume of bite patients; added workload without compensation; high staff turnover; feeling that IBCM is not their responsibility or lacking interest; frustrations from work duplication (already have a reporting system); no accountability or lack of supervisory support; and reluctance to change/adopt a new way of working. Hiring staff addressed many of these barriers since rabies was their primary responsibility. However, this usually required additional funding from research grants or donors, challenging sustainability.

Some programs aimed to use risk assessments for more judicious use of PEP. This was typically in locations with frequent shortages or extremely high expenditure on rabies biologics. These programs often experienced the challenge of ensuring health workers could perform risk assessments to a sufficiently reliable and effective level for PEP to be withheld or discontinued. While some health workers were proficient in using WHO protocols to assess wound severity (Category I, II, and III), others required multiple training sessions. Several health workers were not familiar with the clinical signs of rabies in animals or the importance of assessing the risk of rabies through the status of the biting animal:

> *"The main issue is that it has been difficult for the nurses to perform high-risk assessments... a lot of the cases they post in the peer-support chat are not high-risk based on our definition. And when you look at the protocols of the Department of Health, they actually have a lot more criteria on what is considered high-risk, which concentrates on the nature of the wound rather than the animal status. So, it seems to me that the nurses are still following that protocol in particular."* (Expert #15, Local level)

Significant challenges were also encountered by some when introducing protocols for the judicious use of PEP. These included there being no legal basis for determining PEP decisions from risk assessments; and health workers' hesitancy to withhold or discontinue PEP, even where there was no apparent risk. The provision of hard copy protocols and routine training and communication often facilitated health workers' ability to determine low-risk vs high-risk bites more accurately and make treatment decisions. In addition, programs using an App that automatically assigned the case definition of the animal greatly improved the accuracy of risk determinations and communication with clinical staff and bite patients.

PEP Provisioning

Most experts expressed that the level of PEP provisioning influenced health-seeking behavior, adherence, and the number of bite patients that present to health facilities. Free PEP policies reportedly increased accessibility and adherence to vaccine regimens. However, the provision of free PEP could also lead to a much higher throughput of patients and sometimes an excessive workload for those performing risk assessments. In addition, the demand for PEP frequently remained high even when the risk of rabies was very low or even zero.

According to study findings, health-seeking and PEP adherence typically are much lower where patients must pay for PEP or where travel costs are high due to limited PEP accessibility and availability. These settings often have a lower throughput of patients, with a larger proportion of those presenting as very high risk, as patients tend to make their own risk assessment after a bite event. A few experts said that despite limited access to PEP being an issue, IBCM was often easier to implement in these settings due to self-triage of risk of exposure and a lower number of healthy bite presentations:

> *"Of the people presenting for post-exposure prophylaxis, we're probably looking at about half of them being bitten by dogs that we would consider to be high-risk, and likely to be rabid. We don't see a lot of patients, but the patients that we see have a high chance of being really at risk for rabies. So, the workload is sort of manageable, but every patient is a real priority*

> *because of the risk they're at."* (Expert #5, International level)

In most countries, experts reported that the regions most at risk for rabies were rural areas where people had poor access to health services and may seek out traditional healers after being bitten. This also may affect the performance of health facilities supplying PEP as sentinels for high-risk bites. Thus, some experts stated that improving PEP access could use up a large portion of rabies funding but lead to diminishing returns. Alternatively, they felt that investment in mass dog vaccination could decrease the incidence of rabies in source populations.

Animal Investigation

Barriers to conducting animal investigations using a government workforce were similar to those reported for risk assessments. Experts stated that when an investigation was triggered, oftentimes they were not conducted, were conducted too late, or there was no follow-up after the 10-14 day observation period. Factors contributing to this included: required time/travel/resources (fuel, transport etc.); lack of personnel; high staff turnover; prioritizing diseases considered more economically important in livestock and poultry (e.g., foot-and-mouth disease, avian influenza, lumpy skin disease); lacking formal training as a veterinarian; and/or not feeling comfortable handling animals. Typically, the person designated to investigate the animal had a background and responsibilities unrelated to animal rabies control and did not feel rabies was their job:

> *"The problem is that these inspectors can be veterinarians, biologists, environmental engineers, or what they call 'technicians' without formal training. When they are biologists, they spend most of their time doing vector surveillance. If they are environmental scientists and engineers, they're more interested in water or restaurant inspection. All these activities are what one inspector must do in every district. When there is a veterinarian usually there is more focus on rabies."* (Expert #9, National level)

Hiring program staff resolved many of these issues but required funding. Given that rabies programs are usually not prioritized and are underfunded globally, experts reported this was not always an option and/or sustainable solution. Hired investigators also reportedly felt more confident handling animals and collecting samples, although hands-on training improved these skills for government investigators. Both hired and government staff experienced similar challenges during investigations. These included not being able to find or identify the biting animal or collect a sample because the animal was already killed, buried, or decomposing by the time of the investigation.

Some countries had only one central diagnostic laboratory with limited capacity in terms of equipment, staff, and quality control. Samples sometimes had to be shipped long distances by plane or bus, without cold chain or costs covered. Often, this limited sample submission to areas near the laboratory. IBCM programs implemented in locations with established diagnostic capacity had a significant advantage. Furthermore, programs that trained field staff to use hook and straw sampling techniques simplified procedures and facilitated animal sample collection, storage, and shipping.

Different opinions were expressed about the use of rapid diagnostic tests (RDTs). Some experts stated that RDT results are not reliable and pose complications to protocols for treatment decisions in the case of false negative test results. Moreover, RDTs are not yet recommended by WHO and OIE, thus there is no guidance available for practitioners. On the contrary, other experts found RDTs to be a facilitator for implementing IBCM, by giving more power to the animal health sector and encouraging/empowering them to collect samples by providing immediate results that could be communicated with the health sector and communities:

> *"The vets applied rapid test kits, which are not validated yet, but it was very good to give the vets something at hand to empower them. I think the veterinary system is usually less financed than the human health services… If you want to apply 'One Health' you should actually empower them to bring them closer to the human health services. Otherwise, it is a mismatch between roles and I think this test balanced it out a bit, so the vets had something to motivate the human health services to communicate with*

> *them."* (Expert #7, National level)

Protocols usually stipulated that all samples tested with RDTs should be confirmed with laboratory diagnostics and that PEP decisions should not depend on RDT results. Experts stated that RDT results generally matched laboratory results.

Experts noted that motivation to investigate commonly increased only after a human death or several animal cases in their area. Moreover, IBCM typically increased detection resulting in a swift rise in cases, which can be a disincentive for governments and control programs, especially when approaching elimination. Sometimes animal investigators would be blamed for this rise in cases, which discouraged their future reporting. Experts articulated the importance of preparing leadership prior to implementing IBCM to make sure they understood why they should expect increased cases and that this provides better guidance for control.

The Use of IBCM to Facilitate One Health Collaborations

Barriers to collaboration between sectors were found at the national, regional, and local levels. Government ministries were rarely structured to facilitate intersectoral collaboration and faced challenges getting sectors to work together. Typically, sectors had unbalanced power, with the human health sector having more resources in terms of funding and influence. The priority placed on national rabies programs varied between countries and was often neglected by both sectors. Pre-existing One Health programs that could be used as a resource for IBCM activities were reported to be a significant advantage. Also, programs that involved all relevant sectors in joint discussions, decisions, and training experienced more success:

> *"You need to have the buy-in of both the health and veterinary sectors, from the national to the local level. Because if they don't think it's important then we cannot force them to implement IBCM. They have to better understand why it is important so that it translates to actual work. If the National Program doesn't believe in it, then it is pointless to push it further. But if they recommend IBCM as a policy, then it should go down the line from national, regional, to local government."* (Expert #2, International level)

Experts talked about the difficulty of creating local ownership and changing routine behaviors for information sharing at the individual level up to the ministerial level. There were barriers to getting the health sector to report high-risk bites to their animal health counterparts and to consider investigation results when making patient treatment decisions. In a few instances, local government staff had limited data management skills which made it hard to link human bite cases to animal investigations. Experts mentioned how difficult it is to establish and maintain a line of communication between sectors.

To overcome these challenges, experts emphasized the importance of providing regular feedback and establishing a rapport between human and animal health workers, IBCM staff, and other stakeholders. Additionally, experts reported the need to consider local context and adapt protocols accordingly. Innovations, such as using hotlines as the link between sectors and the community, or developing different protocols for urban and rural settings, helped to facilitate participation from both sectors. Lastly, a couple of countries facilitated a One Health collaboration by employing veterinary staff within the public health system (e.g., Brazil), which is a strategy also used in many high-income countries (e.g., the United States).

Data Reporting and Mobile Technology

Experts reported a common barrier was a lack of data submission from both the human and animal health sectors. Many times, the protocols for the risk assessment and all steps of the investigation (e.g., quarantine/follow-up, sample collection) were completed, but the results were not reported, nor was feedback provided to other sectors.

The use of mobile applications for data reporting and management created both challenges and opportunities. App development initially took a great deal of time and many iterations. Yet once finalized, apps enabled IBCM protocols to be standardized by providing a template for questions and procedures for the risk assessment and animal investigation. Experts said the app allowed real-time data to be accessed remotely by program managers, making it easier to rapidly identify and respond to high-risk cases. Apps also facilitated the timely provisioning of feedback to stakeholders and communities about the risk of rabies and the progress of the control program:

> *"The protocol is what matters - the SOPs and the investigation response requirements. That is what is needed for IBCM to be able to operate, whether you have an app or a piece of paper… The apps allow the technical expertise to sit anywhere in the world and real-time monitor cases, [human] vaccinations, dog vaccination programs... In the past, it would take 2-3 years to get all of this paper data, enter it, and start to learn anything from your system. This ability to real-time evaluate and monitor what's going on and make adjustments is invaluable."* (Expert #1, International level)

While programs using mobile apps experienced issues with network coverage and internet access, these barriers were overcome with an app feature allowing data to be saved. Not all program staff had access to smartphones where the app could be downloaded, which required some programs to purchase tablets or work phones. In addition, experts mentioned there was reluctance from some staff to use the app. Older staff in particular experienced difficulties using this technology and often required additional proficiency training. Changes in technology meant apps frequently needed to be re-downloaded/updated or risked becoming obsolete.

Most experts felt apps were a solution to many issues, while a few experts saw them as an added complexity to training and implementation. In many settings, mobile apps helped to overcome language barriers and could be tailored to local contexts (language, geo-hierarchy etc.). Yet one expert said the use of a mobile app would be difficult in their setting due to high illiteracy in official and local languages.

2.4.2 Impact of COVID-19

IBCM programs encountered COVID-19-related obstacles on several levels. Some programs start dates were postponed, and most training for ongoing programs were postponed or cancelled in 2020 and 2021. Moreover, allocated time and resources (personnel, diagnostics, vaccine storage, surveillance efforts, supply chains, funding) were re-focused on COVID-19:

> *"I think the main impact that COVID-19 is going to have on rabies in [country] is that it's going to hide the problem. Because the surveillance system stops - it's now focused on COVID... most of the resources for the lab go to COVID. And let's say on a regular basis rabies is really neglected - now it's going to be even more neglected."* (Expert #11, National level)

Increased pressure on the health sector meant many health workers were extremely busy and did not report high-risk bites as frequently. Local travel restrictions limited in-person animal investigations or prevented them entirely. Experts in some countries observed drops in animals tested due to decreased surveillance efforts. Several IBCM programs experienced declines in bite patient presentations, typically for 2-5 months at the start of 2020 lockdowns. Experts similarly described the cancellation or disruption of dog vaccination campaigns in 2020 and/or 2021 resulting in lower vaccination coverage. Some of these areas are already seeing rising human rabies deaths and dog rabies, further necessitating the need for IBCM.

Lastly, the pandemic affected peoples' livelihoods and caused income losses, making healthcare less affordable. Experts speculated that people are not feeding community dogs as frequently, leading them to roam further for food and creating a more favorable environment for rabies transmission. People were reported to have also been abandoning pets due to costs and fear of COVID-19 transmission, potentially increasing stray dog numbers. In order to accurately measure the impact of the pandemic, enhanced surveillance such as IBCM is needed.

2.5 Discussion

2.5.1 Key Findings

This study demonstrated the variation between IBCM programs reported across epidemiological and geographical settings. Specifically, the interviews highlighted the diversity within experts' conceptualization of the definition and roles of IBCM. This range of perspectives demonstrates that there are different ways of organizing IBCM within health systems and that it is not a one-size-fits-all approach. While there was consensus among experts and the wider literature about the required components (inputs and activities) of IBCM (**Figure 2.1**) which aligned with WHO guidance (WHO TRS, 2018), these components were operationalized differently between programs. Moreover, experts' perspectives of the purpose of IBCM often differed and by implication, so did the desired outcomes of each program. In practice, IBCM was tailored to meet the demands of the local context and the level of rabies control in place. Experts were well versed in how IBCM operated in their settings and what outcomes they wished to achieve by implementing this One Health approach. But experiences did not necessarily translate across contexts, affecting perceptions about the function, motivation for, and implementation of IBCM. Nonetheless, despite differences in operationalization and desired outcomes, programs shared many similar experiences with the challenges they faced and progress in overcoming them.

Contextual features of each location—which can be described broadly as epidemiological or non-epidemiological (Craig *et al.*, 2018)—contributed to differences in desired outcomes and barriers and facilitators to implementation. The epidemiological context (e.g., human deaths, incidence in the dog population, etc.) partially influenced how much rabies was prioritized at the national and local levels. However, most variation in terms of the success of IBCM and the impact achieved was due to the non-epidemiological context. This includes features such as social and economic (e.g. health-seeking behaviors, GDP, HDI); cultural (beliefs, attitudes, and practices among policymakers, practitioners, communities); geographical (e.g. urban vs. rural, accessibility); service and organization (e.g. motivation, willingness to change); policy (PEP provisioning); financial (e.g. rabies funding); political (e.g. level of decentralization, distribution of power among sectors/stakeholders); and historical (e.g. presence of rabies, progress towards elimination). The issue of sustainability was at the core of many barriers to implementation, which is acknowledged in the literature as a major hindrance to other evidence-based interventions (Hailemariam *et al.*, 2019). For IBCM, using an existing government workforce for program activities was typically seen as a more sustainable option. Yet, experts found it difficult to incentivize or motivate human and animal health workers to change their way of working and complete extra work without supplemental pay. The overall success of IBCM programs appeared to be influenced by practitioners' and stakeholders' viewpoints of the added value of IBCM relative to the extra time and effort required from them and ultimately the degree to which funding is allocated.

Most programs operated in settings with endemic dog rabies, a weak or non-existent surveillance system, and scarce funding available. Thus, the primary desired outcome of these programs was to enhance surveillance cost-effectively to readily identify high-risk human exposures and rapidly locate potential rabid animals. One exception was the IBCM-like approach used in three southern states in Brazil, where dog rabies has been eliminated and strong surveillance already exists. Instead of surveillance, their desired outcome was to reduce the indiscriminate use of PEP following a shortage. Judicious use of PEP was considered a pivotal role for some IBCM programs (e.g., Bali, Haiti, Philippines) while being of minimal importance to others (e.g., Goa, India). In general, countries where frequent PEP shortages occur and/or governments pay for PEP placed more emphasis on its judicious use. Though, that was not always the case. Both India and the Philippines have high numbers of patients receiving government-supplied PEP for healthy animal bites. Yet, in India, where they affordably manufacture their own human rabies biologics, there was no aim to reduce unnecessary PEP. Furthermore, certain country contexts made implementing IBCM challenging. For example, in India where unowned and homogeneous-looking dogs limited the ability to trace animals. Also, in extremely resource-poor countries (e.g., Chad, Madagascar) where there was inadequate infrastructure and more pressing priorities other than rabies. Alternatively, some contextual features made implementing IBCM more straightforward, such as countries in Latin America (e.g., Brazil, Peru) that have substantial budgets for mass dog vaccination, and a strong history of One Health in action facilitating successful rabies control.

2.5.2 Wider Context

This study underscores the complexity of IBCM which stems from the interaction of its many components as they relate to the context or system where they are implemented (Hawe *et al.*, 2015). These findings demonstrate the importance of transferring the evidence base of the IBCM approach to inform adaptations when implemented in a new context to ensure effectiveness (Copeland *et al.*, 2021). Tools used for reporting intervention adaptations, such as the ADAPT guidance, provide a framework and checklist facilitating the streamlining of these processes and reducing research waste (Moore *et al.*, 2021). To prevent misunderstanding of the concept of IBCM, it may be helpful for future guidance to include an explicit program theory (Rodgers & Funnell, 2013), articulating how IBCM is expected to contribute to a chain of intermediate results and ultimately to expected outcomes (via a Theory of Change). This Theory of Change (similar to **Figure 2.2**) has the potential to illustrate to stakeholders how implementing IBCM can be useful in their context and might help overcome challenges specific to their setting. Furthermore, WHO TRS and *Zero by 30* guidance should be expanded to include clear examples of how IBCM has been operationalized in various settings and how activities, outcomes, and aims might differ accordingly. This guidance should include standardized practices for to interpreting rabies risk to improve data quality and comparability of the burden of rabies, transmission pathways, etc. in different settings. Lastly, guidance should be provided for practitioners on the use of RDTs, as well as for health workers receiving patients to cover assessment of the history and signs of rabies in biting animals, which is not integrated into WHO guidance on post-exposure prophylaxis.

Since the approach is complex and relatively new, IBCM exemplifies the challenges faced when implementing One Health approaches (Hampson, De Balogh *et al.*, 2019), with lessons that could be applied to other complex zoonotic diseases. Integrated One Health approaches are vital for tackling both endemic and emerging zoonoses and for antimicrobial resistance (Destoumieux-Garzon *et al.*, 2018; Mackenzie & Jeggo, 2019). Strengthening surveillance systems in LMICs for endemic diseases, such as rabies, builds foundations to address emerging zoonotic diseases like COVID-19 (Halliday *et al.*, 2012). Formalizing One Health approaches through intersectoral government bodies, including joint budgets and policies, can help to overcome institutionalized/ structural barriers (Mackenzie & Jeggo, 2019; Halliday *et al.*, 2012). Yet, like IBCM, varying perceptions about the concept of 'One Health' make it difficult to standardize the operationalization of these approaches in both high-income countries and LMICs (Lerner & Berg, 2015; Evans & Leighton, 2014). These challenges are amplified by the lack of sustainability of funding and infrastructure that are exacerbated in LMICs. This study emphasizes the need for more implementation research to improve and understand IBCM program delivery and policies (Theobald *et al.*, 2018). In recent years, such studies have helped strengthen the gap between knowledge and real-world action for a variety of neglected tropical diseases (Bardosh, 2018; UNICEF *et al.*, 2021). Future research exploring the knowledge-practice gaps of implementing IBCM could improve the cost-effective rollout of IBCM and provide a potential example for other One Health interventions.

2.5.3 Strengths and Limitations

There are some limitations in this study. One-hour interviews were a short time to discuss perspectives of and experiences with IBCM. For broader comprehension of the implementation and adaptation of IBCM, more in-depth qualitative research is required (e.g., ethnographic participant observations, and development of program theory) (Hailemariam *et al.*, 2019). This study was not designed to be representative of IBCM programs or specific regions/countries. Each participant was only expressing their own opinion and experience. Hence, caution is required regarding the interpretation of the study’s representativeness and reliability. Most participants had a background in veterinary medicine or epidemiology, and representation from the medical sector was lacking. Future research including the perspectives of clinicians and public health experts would be important, however, it should be noted that there is relatively little involvement at the national and international level of medical professionals leading One Health programs for rabies. The logic model of IBCM (**Figure 2.2**) serves as a template but does not fully describe the complexity of IBCM and how that relates to different contexts. The integration of process evaluations should help to inform whether the intervention was delivered as intended and if not, why not (Moore *et al.*, 2021). Moreover, the programs included varied in maturity, from a decade in Bali, Indonesia (2011) to programs still in development, limiting direct comparison. Nevertheless, this study covered a wide scope of perspectives in terms of work experience, epidemiological contexts (from elimination to high endemicity), and geographies across several LMICs. Thus, the study is an important step towards discovering lessons about this relatively new approach and understanding how One Health can be operationalized to achieve dog-mediated rabies elimination.

2.5.4 Conclusions & Recommendations

In conclusion, with preliminary recommendations to support the design and implementation of IBCM programs keeping sustainability in mind. Firstly, as one of the few zoonotic diseases with an official elimination goal set by the WHO, rabies should be better prioritized and funded to support the hiring of staff and implementation of control programs (Zero by 30, 2018). Secondly, a One Health surveillance approach is essential and should be implemented in all endemic countries at any stage of their rabies control program as this is the most targeted way to identify rabid animals. Many existing reporting systems for rabies are not fit-for-purpose for surveillance and provisioning of PEP. Surveillance systems are often siloed and do not consider the risk of the biting animal or recognize the value of risk assessments, leading to the uninformed administration of PEP. In response, the IBCM approach has been developed as a cost-effective way to address these weaknesses (Undurraga *et al.*, 2017). However, current structures within governments, policies, and ways of working pose barriers to introducing IBCM. To successfully and sustainably implement IBCM, there needs to be consideration for how governments and policy can be updated to better facilitate multisectoral, interdisciplinary approaches generally (UNICEF *et al.*, 2021). Thirdly, it is imperative that each program is tailored to the context of the country/region where it will be implemented, with careful consideration of context during development, implementation, and evaluation (Craig *et al.*, 2018). Lastly, the joint involvement and ownership of government authorities from both the health and veterinary sectors, local stakeholders, and the community are essential for the effective development and adoption of IBCM protocols (Masefield *et al.*, 2021; Vanyoro *et al.*, 2019). It is crucial to ensure all partners involved understand the value of IBCM and are prepared to expect a rise in detected rabies cases after implementing IBCM, with reassurance that this information can be used to strengthen their control measures.

CHAPTER 3

Feasibility, fidelity, and adaptation of One Health rabies surveillance: Evaluation of Integrated Bite Case Management implementation in Oriental Mindoro, Philippines

3.1 Abstract

International organizations like the WHO advocate Integrated Bite Case Management (IBCM), a One Health approach, to reach *Zero by 30* rabies elimination goals. Through intersectoral collaboration, IBCM has the potential to enhance rabies surveillance to readily identify high-risk human exposures and investigate biting animals for signs of rabies. In this three-year implementation study, the project team developed, implemented, and adapted an IBCM program in Oriental Mindoro province, Philippines. A mixed methods process evaluation was used to assess: 1) the feasibility of effective delivery of IBCM, in terms of acceptability and appropriateness, barriers and facilitators, and variation between catchment areas; 2) the extent to which IBCM was implemented as intended, or adoption of practices; and 3) how initial IBCM protocols adapted over the course of the study to fit the local context. Data included IBCM surveillance data (e.g. bite patient risk assessments and animal investigations), provincial bite patient and laboratory records, semi-structured interviews, and initial and end of project Theories of Change. Quantitative IBCM data were analyzed for the level of completeness and understanding of protocols. Qualitative interview data were analyzed inductively and deductively using Normalization Process Theory. The evaluation showed that IBCM was not feasible at the beginning of the study. The initial project design envisioned that training would facilitate a rapport between human and animal health workers resulting in collaboration and communication to uptake IBCM protocols. Instead, project staff ended up conducting the majority of activities. Once protocols were adapted to address implementation barriers in 2020, including adjustments for the COVID-19 pandemic, IBCM was delivered more effectively in 2021 and 2022. There was significant variation in the level of effective delivery and adoption of

IBCM between catchment areas due to differences in contextual features and encountered barriers and facilitators. Protocols and procedures were continuously adapted to the local context throughout the project by both project staff and participants. IBCM showed great promise as an effective intervention to enhance rabies surveillance in the Philippines, being perceived as highly acceptable by participants. However, several challenges were identified with the appropriateness of protocols for the setting, and participant's ability to adopt IBCM practices. This limited the extent of effective delivery and the aim of developing best practice for nationwide IBCM implementation. However, evidence generated by this study provided key lessons for adapting IBCM guidance for expansion to other provinces in the Philippines.

3.2 Introduction

Despite being virtually 100% vaccine-preventable with timely administration of post-exposure prophylaxis (PEP), rabies virus kills an estimated 59,000 people annually throughout the world (Hampson *et al.*, 2015). While rabies is a zoonotic disease capable of infecting and being transmitted by any mammal, almost 99% of human deaths are due to bites from rabid dogs (WHO Rabies Modelling Consortium, 2019). High-income countries have eliminated dog-mediated rabies through animal control policies and mass dog vaccination (MDV) (WHO TRS, 2018). Yet, many low- and middle-income countries (LMICs) are still endemic, including the Philippines where reported deaths continue to fluctuate between 200-300 annually (Philippines DOH, 2020).

In the Philippines, rabies elimination policies have been enacted as far back as the American colonial period, with awareness campaigns, culling of stray dogs, muzzling laws, and monitoring/reporting of human cases implemented between 1910-1934 (Cruz *et al.*, 2019). Since then, anti-rabies initiatives have ebbed and flowed over the century, with intersectoral nationwide rabies control measures re-established in 1991 (NRPCP Strategy, 2020). In 2007, the Philippines Government enacted the Anti-Rabies Act (Republic Act No. 9482) mandating the implementation of the National Rabies Prevention and Control Program (NRPCP) from the national to the barangay (village) level which aimed to eliminate rabies by 2020. With the politically decentralized system of governance in the Philippines, the power to act on anti-rabies measures was formally delegated to local government units (LGUs). The comprehensive NRPCP strategy involves multi-sector, inter-agency i.e. Department of Health (DOH) and Department of Agriculture (DA) collaboration and allocated funding to support program activities, such as vaccination, public awareness campaigns, and expansion of infrastructure. Despite the NRPCP catalyzing control efforts, outbreaks continue and only a few islands and provinces have been declared rabies-free (NRPCP MOP, 2019). Therefore, NRPCP initiatives and the elimination goal have been extended to achieve zero human deaths from dog-mediated rabies by 2030 (DOH 2019), in line with the global *Zero by 30* strategy (WHO, FAO, & OIE, 2018).

A key component of the Anti-Rabies Act of 2007 was the decentralization of PEP provisioning through the widespread establishment of >500 Animal Bite Treatment Centers (ABTCs), mandating they carry adequate PEP supply for bite patients, typically for free (Amparo *et al.*, 2018). The extremely high incidence of bite patients presenting to ABTCs, exceeding 800/100,000 persons annually in some provinces, is mostly due to bites from healthy dogs (Quiambao *et al.*, 2020) with PEP administered to nearly all bite victims if available. While this free PEP policy has improved accessibility, it has also resulted in a continuous and unsustainable rise in PEP seeking, even with a reduced circulation of rabies in some provinces due to MDV campaigns (Rysava *et al.*, 2019). Records from the DOH (2020) show that the number of animal bite incidents reported nationally has increased almost seven-fold from the start of the NRPCP in 2007 (176,501 bites) to a decade later in 2017 (1,229,607 bites). The high costs of PEP, along with the exponential increase in demand, have put substantial strain on local and national healthcare budgets (Oriental Mindoro PHO investment plan, 2020).

Meanwhile, routine rabies surveillance data is not sufficiently sensitive for international agencies to verify rabies freedom. Three primary information systems are used for rabies surveillance in the Philippines: 1) the Philippine Integrated Disease Surveillance and Response (PIDSR) system, for human cases; 2) the Philippine

Animal Health Information System (Phil-AHIS), for animal cases, and 3) the National Rabies Information System (NaRIS), to record PEP usage. Data entered into these systems are not integrated or shared between sectors, and several issues exist challenging data quality. While typically conducted thoroughly, investigations are usually only initiated after a human fatality, impeding the detection of the responsible rabid dog and limiting effective preventative action for other exposed persons or animals. Diagnostic testing of animals is often conducted through population-based sampling—an ineffective method no longer recommended for rabies (WHO TRS, 2018) due to the low incidence of infection and short time window for diagnosis (Hampson *et al.*, 2016). Moreover, passive reporting of suspicious animals is rare because it depends on community awareness, motivation, and the ability to detect and report rabid dogs. Hence, current surveillance only detects a small proportion of circulating animal cases (Swedberg *et al.*, thesis Chapter 4).

Current rabies surveillance systems in the Philippines, and national procedures for managing bite victims and for epidemiological investigation are outlined in **Figure 3.1**. There are three distinct government ministries (systems) with delegated responsibilities for rabies prevention and control: human health, epidemiology & surveillance, and veterinary & agriculture. Each system is siloed, with limited or no intersectoral collaboration or shared reporting of data. Typically, bite patients are referred from Rural Health Units (RHUs) or present directly to ABTCs where they receive wound care and PEP is administered. While protocols state PEP should only be provided to Category II and III exposures, this decision is largely at the discretion of staff and varies by ABTC, with PEP commonly administered for Category I (non-exposure) events. The patient then returns to the ABTC for subsequent PEP doses following the 4-dose Thai Red Cross intradermal (ID) regimen (day 0, 3, 7 and 28) (Khawolod *et al.*, 2006). Data on PEP usage for each bite patient is submitted in the NaRIS and electronic records are available to the Provincial Health Office (PHO) and DOH. If a patient presents to a health facility with symptoms of rabies, palliative care is provided and an investigation is conducted by the Provincial Rabies Coordinator, typically involving staff from both the PHO and the Provincial Veterinary Office (Pro-Vet), with results recorded in the PIDSR system. If the biting dog/animal has been killed, the veterinarian is expected to collect a sample and submit it to the regional laboratory for diagnostic testing, with results recorded in Phil-AHIS.

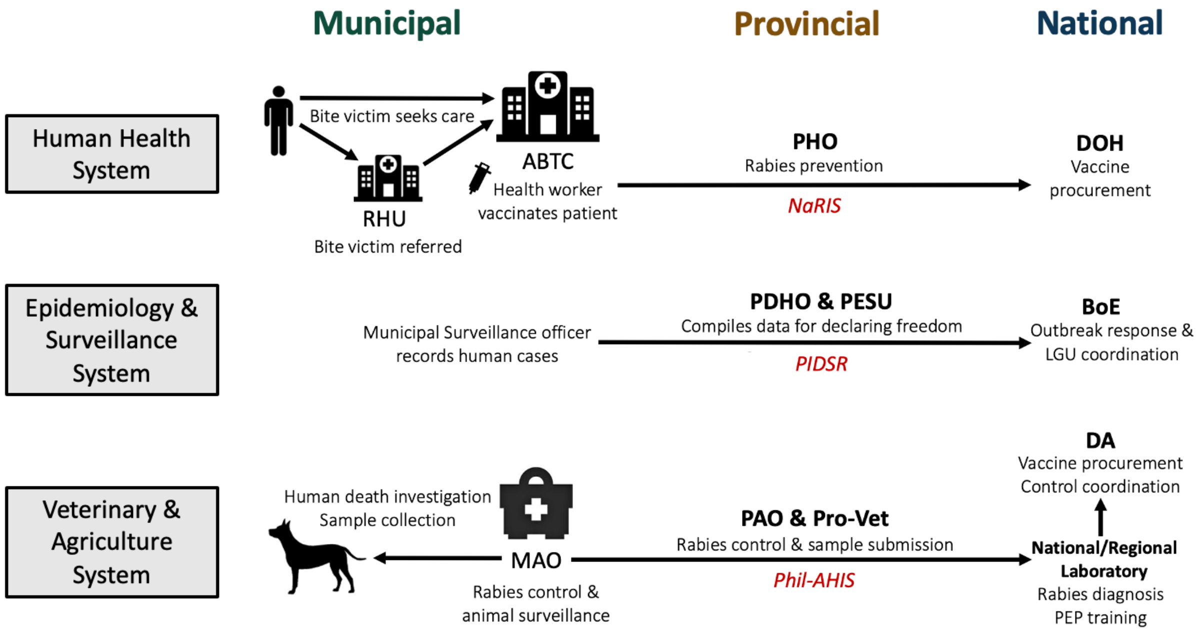


Figure 3.1 - Current national procedures for bite patient management and rabies surveillance in the Philippines. RHU=Rural Health Unit; ABTC=Animal Bite Treatment Center; PHO=Provincial Health Office; DOH=Department of Health; PDHO=Provincial Department Health Office; PESU=Provincial Epidemiology & Surveillance Unit; BoE=Bureau of Epidemiology; LGU=Local Government Unit; PAO=Provincial Agriculture Office; Pro-Vet=Provincial Veterinary Office; Information Systems; NaRIS=National Rabies Information System; PIDSR=Philippines Integrated Disease Surveillance & Response; Phil-AHIS=Philippine Animal Health Information System.

Weak surveillance and ineffective administration of PEP are commonplace in rabies-endemic LMICs. To address these challenges and support LMICs in achieving 2030 elimination goals, international organizations developed *Zero by 30*: The global strategic plan to end human deaths from dog-mediated rabies by 2030 (FAO, OIE/WOAH, WHO, & GARC, 2018). Central to this strategy's framework is the concept of One Health, recognizing the interconnectedness between the health of humans, animals, and their shared environment (FAO, UNEP, WHO, & OIE/WOAH, 2022). The approach, Integrated Bite Case Management (IBCM), is advocated as a potential solution to sufficiently enhance surveillance to enable verification of rabies freedom (Wallace *et al.*, 2015; Hampson *et al.*, 2016) and reduce the costs of PEP once rabies has been controlled (WHO TRS, 2018). IBCM formally engages human and animal health sectors (‘One Health’) to assess the risk of genuine exposure to rabies; determine the subsequent need for PEP; and rapidly identify rabid animals. Implementation of IBCM in Haiti, a resource-poor setting, improved patient care (Etheart *et al.*, 2017), whilst reducing PEP use by 40-60% (Undurraga *et al.*, 2017). However, in endgame settings (i.e. some Philippines provinces) where rabies incidence is very low or potentially absent, PEP savings are expected to be even higher. Thus, IBCM could have immediately beneficial applications within the Philippines and be of critical importance in eliminating human rabies deaths by 2030.

As a complex intervention (Hawe *et al.*, 2015), IBCM has several components interacting between multiple sectors and stakeholders which aim to achieve numerous variable outcomes. Therefore, the operationalization of IBCM is likely to vary in different contexts (Swedberg *et al.*, 2022). When evaluating a complex intervention, the UK Medical Research Council (MRC) Guidance recommends using a systematic approach, meaning the steps of the process are clearly defined and can be replicated (Skivington *et al.*, 2021). This approach should involve close collaboration with local stakeholders throughout the implementation of the intervention to ensure adequate monitoring and adaptation, including the creation of a theoretical understanding of how the intervention will operate in its setting, such as a Theory of Change (ToC) (Rodgers & Funnel, 2013). In addition, the intervention should be piloted to evaluate the feasibility of delivery and adaptation of protocols prior to scaling up implementation. Currently, there is no guidance for the operationalization of IBCM for local contexts or how to tailor protocols for effective implementation.

Following UK MRC Guidance, this study describes the development and adaptation of the IBCM intervention over three years. Here, a process evaluation of IBCM implementation was conducted in the province of Oriental Mindoro, Philippines to determine whether activities were implemented as intended in initial protocols and resulted in the outputs (i.e. quantitative results from activities) and outcomes (i.e. the change that occurs following activities/outputs) described in the initial project ToC created during the development phase of the study in 2019 (**Table 3.1**, *Appendix 5*). In this chapter, the aim was to identify key lessons for adaptation of IBCM implementation for scaling up and integration into national policy. The study objectives were to assess: 1) the feasibility of effective delivery of IBCM, in terms of acceptability and appropriateness, barriers and facilitators, and variation between catchment areas; 2) the fidelity, or extent to which IBCM was implemented as intended and adopted as a routine practice; and 3) how initial IBCM protocols were adapted over the course of the study to fit the local context.

3.3 Methods

3.3.1 Design & Setting

This is a process evaluation of a three-year implementation study of the IBCM intervention in the rabies-endemic province of Oriental Mindoro from January 2020 to December 2022. The overarching aim of the study was to deliver a cost-effective, epidemiologically robust surveillance package to guide and sustain the elimination of canine rabies from the Philippines. Here, a mixed methods study design was chosen because it is recognized as best practice for evaluating the implementation of complex interventions (Kiely *et al.*, 2021) to understand to what extent study objectives were achieved and interpret why this was.

Study Setting

Oriental Mindoro is one of two provinces located on the Island of Mindoro, covering the eastern half, with the adjacent province Occidental Mindoro covering the western half (**Figure 3.2**). These two provinces, in addition to three others (Marinduque, Romblon and Palawan) comprise Region IV-B, MIMAROPA of the Philippines. Located 140 km southwest of Manila, Oriental Mindoro consists of 15 municipalities and a human population of 908,339 (Philippines Statistics Authority, 2020). The provincial capital city, Calapan, represents ~16% (145,786) of the total population and is the only urban center. Rabies is endemic in the domestic dog population, with the Provincial Health Office (PHO) reporting animal bites as one of the top morbidities over the last year (>1,000 per 100,000 persons presenting to ABTCs for PEP per year).

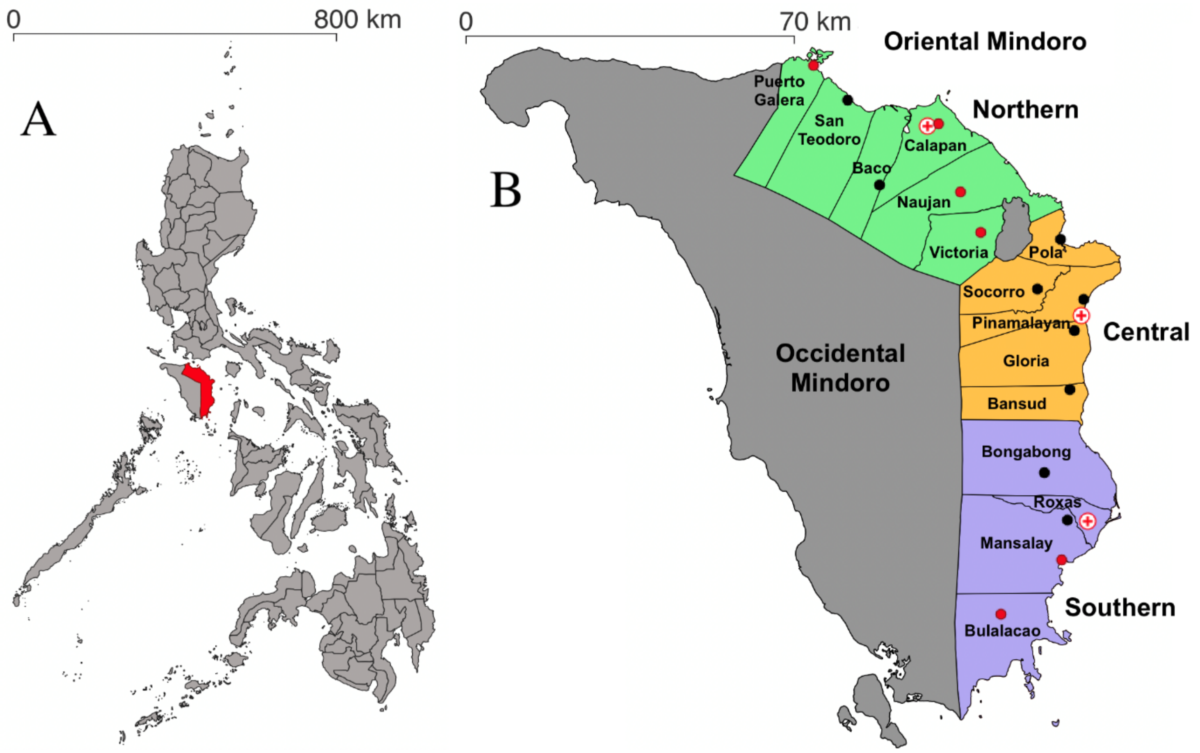


Figure 3.2 - Location of study population and health facilities. (A) Philippine provinces showing Oriental Mindoro (red). (B) Oriental Mindoro Province on the island of Mindoro, showing the three major hospitals with ABTCs (red crosses on white dots), six Rural Health Units (RHUs) with ABTCs (red dots), and nine RHUs (black dots) without ABTCs that refer bite patients for PEP. Shapefiles sourced from UN-OCHA Humanitarian Data Exchange Project (UN OCHA, 2020).

As of 2022, there were nine health facilities with accredited ABTCs administering PEP; three larger hospitals treating the majority of bite patients, and six smaller community-level clinics with lower patient volumes. In addition, there were nine RHUs without ABTCs, providing wound care and then referring patients for PEP. Each municipality has a Municipal Agriculture Office (MAO) in charge of crops, livestock and, to a lesser extent, zoonotic diseases, such as rabies. The MAO, often in coordination with the Pro-Vet, coordinates MDV campaigns and is typically responsible for enforcing responsible pet ownership ordinances. The extent of MAO involvement in anti-rabies activities varies significantly between municipalities depending on the allocated budget and how much rabies is prioritized. The Regional Animal Disease Diagnostic Laboratory (RADDL) for the MIMAROPA region is located just south of Calapan. All rabies diagnostic testing in the province is conducted by RADDL, with staff responsible for guiding the application of government-mandated sample/testing protocols.

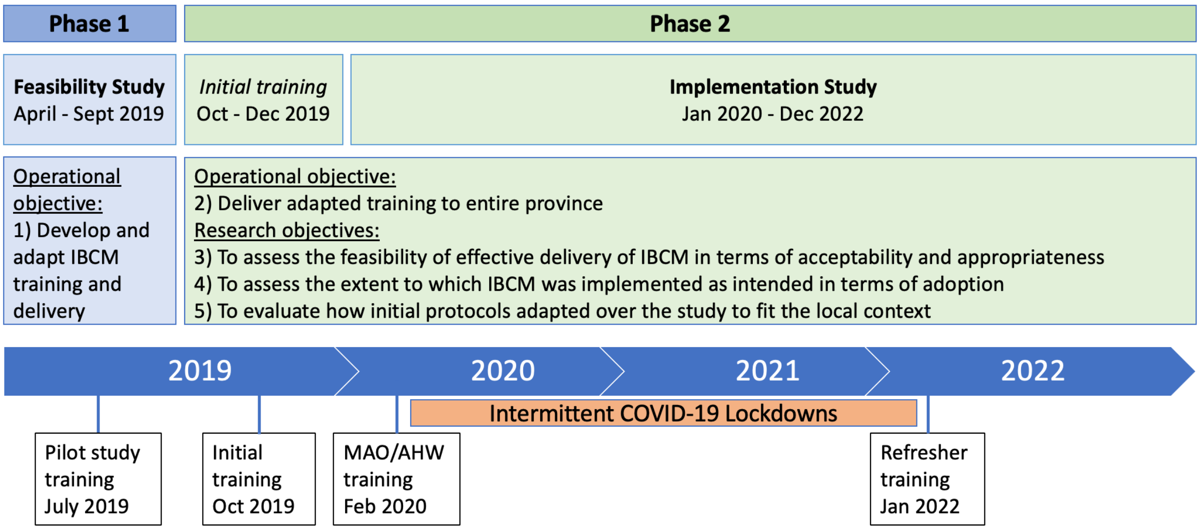
IBCM was implemented in nine catchment areas spanning all 15 municipalities of Oriental Mindoro, where a catchment area is defined by each ABTC, and the patient population and municipalities (i.e. MAO and RHUs) they cover. For the purposes of introducing IBCM, these catchment areas were further grouped into three subregions: Northern (five), Central (one), and Southern (three) (**Table 3.2**). The Northern subregion, comprising the capital Calapan, is the most populous and has the most ABTCs. Whereas, the Central and Southern subregions are more rural and isolated, with fewer ABTCs. During the study, the Central subregion only had one hospital ABTC covering five municipalities and >260,000 people.

Oriental Mindoro Region	ABTCs	Municipalities covered
Northern Population - 408,447 5 ABTCs 2 RHUs w/o 6 municipalities	- Oriental Mindoro Provincial Hospital (OMPH) - Calapan City ABTC - Naujian ABTC - Puerto Galera ABTC - Victoria ABTC	Baco (RHU, no ABTC) Calapan City Naujan Puerto Galera San Teodoro (RHU, no ABTC) Victoria
Central Population - 260,590 1 ABTC 5 RHU w/o 5 municipalities	- Oriental Mindoro Central District Hospital (OMCDH)	Bansud (RHU, no ABTC) Gloria (RHU, no ABTC) Pinamalayan (RHU + OMCDH) Pola (RHU, no ABTC) Socorro (RHU, no ABTC)
Southern Population - 239,302 3 ABTCs 2 RHUs w/o 4 municipalities	- Oriental Mindoro Southern District Hospital (OMSDH) - Bulalacao ABTC - Mansalay ABTC	Bongabong (RHU, no ABTC) Bulalacao Mansalay Roxas (RHU, no ABTC)

TABLE 3.2 - DESCRIPTION OF THE STUDY POPULATION AND HEALTH FACILITIES.

3.3.2 Design of IBCM Protocols and Implementation Study

The study was designed in two phases: Phase 1, a feasibility pilot study in a subset of municipalities in Southern Oriental Mindoro, and Phase 2, an implementation study across the entire province (Northern, Central, and Southern). Shown in **Figure 3.3** is a schematic timeline of activities and an overview of study objectives. Initial protocols and the initial ToC (2019) were developed by the project team (i.e. both University of Glasgow researchers and in-country partners) and local stakeholders. The process evaluation study design and data collection methods (e.g. interview topic guide) were developed by the University of Glasgow research team. Quantitative IBCM data was collected by trained PHWs/AHWs, and the project staff. Interviews were conducted by a single project team member, hired as an in-country social scientist. Analysis of interviews was completed by the PhD candidate, then results were interpreted and discussed by the PhD candidate, the team social scientist, and two senior qualitative researchers working on the project.



Operational objective:
1) Develop and adapt IBCM training and delivery

Operational objective:
2) Deliver adapted training to entire province

Research objectives:
3) To assess the feasibility of effective delivery of IBCM in terms of acceptability and appropriateness
4) To assess the extent to which IBCM was implemented as intended in terms of adoption
5) To evaluate how initial protocols adapted over the study to fit the local context

FIGURE 3.3 – TIMELINE AND OVERVIEW OF STUDY ACTIVITIES, RESEARCH OBJECTIVES, AND OPERATIONAL OBJECTIVES.

Study IBCM Protocols

In line with the latest WHO technical guidance (WHO TRS, 2018), current procedures in the Philippines for bite patient management and rabies surveillance were enhanced through the integration of revised protocols using an IBCM strategy (**Figure 3.4**). Steps one through four of the augmented surveillance protocols comprise IBCM response activities conducted in collaboration with project-trained staff from human and animal health sectors ('One Health'). Protocols for augmented IBCM steps are as follows (SPEEDIER Study Protocols v9, 24 June 2022):

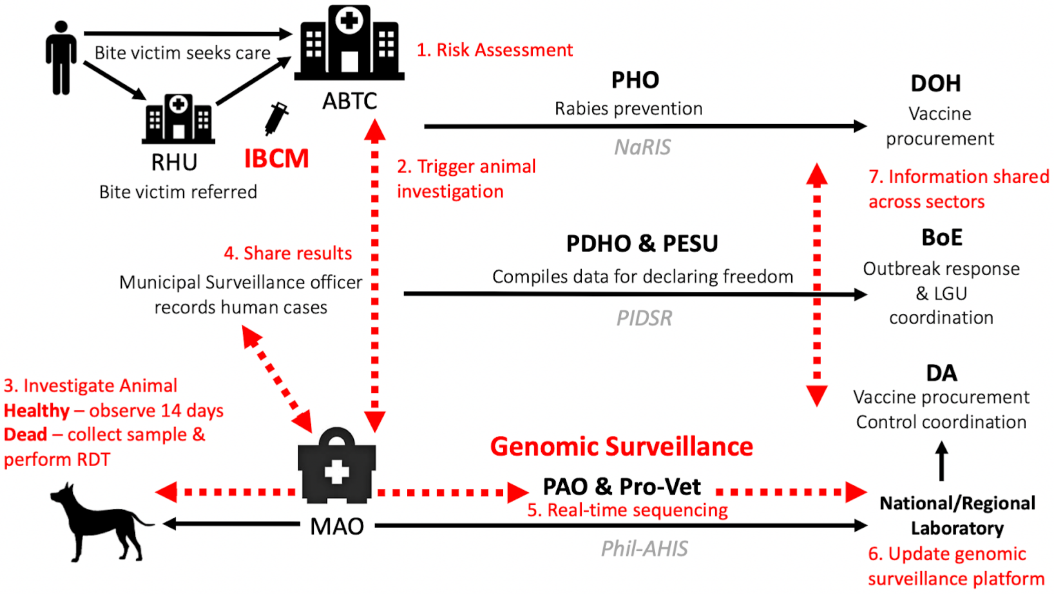


FIGURE 3.4 – REVISED IBCM PROTOCOLS INTRODUCED IN ORIENTAL MINDORO. Current government procedures in the Philippines (shown in black) and augmented IBCM project activities (shown in red) for bite patient management and rabies surveillance. IBCM activities are represented in steps 1 to 4. Genomic Surveillance steps are represented in steps 5 to 7. RHU=Rural Health Unit; ABTC=Animal Bite Treatment Center; PHO=Provincial Health Office; DOH=Department of Health; PDHO=Provincial Department Health Office; PESU=Provincial Epidemiology & Surveillance Unit; BoE=Bureau of Epidemiology; LGU=Local Government Unit; PAO=Provincial Agriculture Office; Pro-Vet=Provincial Veterinary Office; Information Systems; NaRIS=National Rabies Information System; PIDSR=Philippines Integrated Disease Surveillance & Response; Phil-AHIS=Philippine Animal Health Information System.

Step 1: Bite Patient Risk Assessment

When a bite patient presents to a health facility (RHU or ABTC) the staff—referred to collectively as public health workers (PHWs) here—should carry out a risk assessment based on the history of the biting animal and circumstances of the exposure. In addition to baseline data collected for NaRIS, the risk assessment involves additional questions assessing the biting animal's vaccination history; outcome (alive, dead, or disappeared); and health status (e.g. healthy, sick, or displaying clinical signs of rabies). The PHW should complete the risk assessment using a form located on a tailored mobile IBCM application (App), to ensure rapid and accurate information recording and standardization of criteria, to facilitate real-time alerts to trigger investigations.

Step 2: Triggering Animal Investigation

According to the risk assessment, a 'high-risk' bite involves animals that die, are killed, disappear, or show signs of illness following the biting incident. In the event of a high-risk bite, the PHW is expected to immediately alert their animal health worker (AHW) counterpart at the corresponding MAO, using the App. The automated real-time alerts generated by the App from the risk assessment data encoded by the PHW will detail information required for the animal investigation (e.g. patient's name/contact information, history of the biting animal, etc.).

Step 3: Animal Investigation

When the AHW receives an alert of a high-risk bite via the App, they should investigate immediately and always within 24 hours. Using the information from the risk assessment, the AHW should interview/follow up with the bite patient, the owner of the biting animal (if known), and any other witnesses or persons/animals that may have been exposed. If a phone call follow-up is unsuccessful or indicates in-person follow-up is necessary, the AHW should visit the dog owner to visually inspect the biting animal. The circumstances of the bite and details of the animal's behavior and health should be recorded according to the criteria on the standardized form, and then submitted via the App. Any animal suspected of having rabies or displaying clinical signs compatible with rabies should be euthanized according to current procedures in the Philippines (NRPCP Manual of Procedures, 2019). If dead or euthanized, the AHW should collect a sample; perform a rapid diagnostic test (RDT) on-site; record the results into the App; and send the sample to RADDL for confirmatory diagnostic testing. Upon completion, all details from the investigation should be submitted to the App, with a results summary automatically sent to the PHW for appropriate patient care and to the Pro-Vet and PHO to guide subsequent control efforts.

Step 4: Feedback and Sharing of Project Results

The project team will provide feedback to PHWs, AHWs, and local stakeholders through routine monthly and quarterly reports summarizing the surveillance data generated through IBCM, and stakeholder meetings will be held to discuss their interpretation. PHWs, AHWs, and stakeholders will also be able to access surveillance data and summaries on the data platform and project website, including time series and maps of bites indicating risk status, investigations undertaken and their outcomes.

Recruitment and Training

The study recruited a minimum of one PHW and one AHW from each of the 15 municipalities to participate in training, along with key local stakeholders from the human/animal health sectors (e.g. PHO and Pro-Vet). Participants were informed on general rabies knowledge, then trained on how to perform risk assessments for bite patients; conduct animal investigations for suspected animals, including sample collection and use of RDTs; and encode data into the bespoke App. During training, the App was downloaded to their personal devices and each ABTC/MAO was provided with a tablet containing the App. All PHWs and AHWs were added to a “peer-support chat” as a resource to ask questions and discuss IBCM (e.g. bite patients, suspected animals, laboratory results, etc.) with other participants in their province, local stakeholders, and project staff.

An overview of IBCM training sessions is shown in **Table 3.3**. All training sessions were facilitated by the in-country project team and provincial or national-level stakeholders. Initial IBCM training commenced in 2019 in each of the three subregions in Oriental Mindoro as in-person two-day sessions with both PHW and AHW participants. In February 2020, an in-person demonstration training for AHWs was conducted by RADDL and Pro-Vet staff, covering animal investigations, sample collection, and the use of RDTs. In January 2021, a one-day joint refresher training was held virtually via Zoom for each subregion.

Training Session	**Dates / Venue**	**Number of PHW / AHW participants attended and municipalities represented**
Pilot IBCM training (Southern)	July 16-17, 2019 Roxas, Oriental Mindoro	12 PHWs, 9 AHWs 4 municipalities (Bongabong, Bulalacao, Mansalay, and Roxas)
IBCM training (Central)	October 7-8, 2019 Calapan, Oriental Mindoro	12 PHWs, 3 AHWs 5 municipalities (Bansud, Gloria, Pinamalayan, Pola, and Socorro)
IBCM training (Northern)	October 9-10, 2019 Calapan, Oriental Mindoro	15 PHWs, 5 AHWs 6 municipalities (Baco, Calapan, Naujan, Puerto Galera, San Teodoro, Victoria)
MAO training: investigation and sample collection	February 27, 2020 Calapan, Oriental Mindoro	0 PHWs, 16 AHWs 11 of 15 municipalities represented (none from Bongabong, Bansud, Calapan or Socorro)
IBCM refresher training (Northern)	January 12, 2022 Virtual - online	5 PHWs, 4 AHWs 6 municipalities (Baco, Calapan, Naujan, Puerto Galera, San Teodoro, Victoria)
IBCM refresher training (Central)	January 19, 2022 Virtual - online	10 PHWs, 11 AHWs 5 municipalities (Bansud, Gloria, Pinamalayan, Pola, and Socorro)
IBCM refresher training (Southern)	January 26, 2022 Virtual - online	7 PHWs, 6 AHWs 4 municipalities (Bongabong, Bulalacao, Mansalay, and Roxas - no PHW representative from Bongabong)

TABLE 3.3 - DETAILS OF IBCM TRAINING SESSIONS IN ORIENTAL MINDORO PROVINCE.

3.3.3 Process Evaluation

Phase 1: Pilot Study of the Feasibility of Delivering IBCM

From April to September 2019, a 6-month feasibility study (Phase 1) was conducted in the subregion of Southern Oriental Mindoro, comprising four municipalities; two ABTCs at the time (three, as of May 2022); and four MAOs. The operational objective was to adapt IBCM protocols, procedures, data collection methods (e.g. the App), and the training package for delivery in Phase 2. In Phase 1, PHWs and AHWs were trained to follow IBCM protocols and how to use the App, then asked to participate in the delivery of IBCM and data collection for evaluation. To identify required refinements, the project team, including the PhD candidate, evaluated training observation data, monitored the peer-support chat, observed participants' experience using the App, and assessed the quantity and quality of data submitted to the IBCM database.

Phase 2: Evaluating IBCM Implementation

In Phase 2, the delivery of IBCM implementation was evaluated in Oriental Mindoro over three years (Jan 2020 to Dec 2022) and the processes by which outcomes were or were not achieved were assessed. Each of the nine ABTC/catchment areas were evaluated using mixed methods. **Table 3.4** summarizes the aspects of IBCM delivery included in the assessment, and the data collected/analysis method used for each. Three primary aspects of IBCM were evaluated: 1) the feasibility of IBCM implementation, or the suitability of IBCM for use in routine practices (Pearson *et al.*, 2020), 2) the fidelity of IBCM implementation, or degree to which PHWs and AHWS implemented IBCM as intended by the initial protocols (Dusenbury *et al.*, 2003), and 3) how initial protocols and procedures adapted over the course of the study to fit the local context. The process evaluation was then used to identify adaptations that were critical for the effectiveness of IBCM delivery and formulate lessons for scale up in the Philippines.

Aspect of IBCM delivery assessed	Data collection methods and objectives	Data used
Feasibility of IBCM delivery I. Acceptability and appropriateness II. Barriers & facilitators III. Variation in contextual factors	Semi-structured interviews with trained PHWs and AHWs to appraise: I. To what extent IBCM protocols were understood, perceived as useful/valuable, accepted, and appropriate for the context II. To what extent barriers and facilitators to effective IBCM delivery were encountered III. How contextual features varied and affected the level of IBCM delivery between catchment areas	Semi-structured interviews with PHWs and AHWs
Fidelity of IBCM delivery (adoption/uptake) I. Quantitative indicators of adherence II. Variation of contextual factors influencing level of adherence	I. Data collected via the App on the number of participants using app and achieved coverage of completed risk assessments (numerator) as a percentage of total patient presentations (denominator) and animal investigations (numerator) as a percentage of total biting animal identified as high-risk (denominator) II. Semi-structured interviews with trained PHWs and AHWs to examine the extent to which IBCM protocols were able to be integrated into routine work and reasons for variation in fidelity between catchment areas and PHWs vs. AHWs	IBCM data: Bite patient risk assessment forms and animal investigation forms Provincial records: PHO bite patient annual reports and RADDL laboratory records Semi-structured interviews with PHWs and AHWs
IBCM protocol adaptations and lessons for scale-up	Theory of Change (ToC) workshop with core project team and local stakeholders exploring how and why activities lead, or did not lead, to desired outcomes	Initial ToC, developed April 2019 by project team Revised ToC, developed May 2022 from project team/stakeholder workshops

TABLE 3.4 - SUMMARY OF RESEARCH METHODS USED TO ASSESS FIDELITY AND FEASIBILITY OF IBCM DELIVERY AND ADAPTATIONS TO PROTOCOLS AND PROCEDURES.

ASSESSING FEASIBILITY OF IBCM DELIVERY

Feasibility of IBCM delivery was assessed using semi-structured interviews (30-45 minutes) conducted with PHWs and AHWs in-person before the COVID-19 pandemic and then over the phone/Zoom following intermittent lockdowns (~February 2020). Typically, interviews were completed 1-2 months after participation in one of the training sessions listed in **Table 3.3**. Interviews with the primary PHW or AHW responsible for IBCM activities were requested first, but if they were not available or refused, the next relevant participant was invited to interview.

Using these data, feasibility was assessed in terms of acceptability and appropriateness, then reviewed to identify varying contextual features, and barriers and facilitators specific to each catchment area and sector. A topic guide shown in **Table 3.5** (*Appendix 6*) was created as part of the study design and used to guide each interview. During interviews, participants were asked about their/colleagues' understanding of and perceived value of IBCM; how IBCM differed from their usual way of working; and if they believed they could integrate IBCM into their existing work routine.

ASSESSING FIDELITY OF IBCM DELIVERY

To assess the fidelity of IBCM delivery, quantitative indicators were used to calculate data completeness and examine the extent to which protocols were adopted and/or adhered to in different catchment areas. Protocols used for this included: every bite patient presenting to the ABTC should have a risk assessment performed, then encoded in the App; all high-risk bites should have an animal investigation conducted, then encoded in the App; and sample collection, RDTs, and confirmation testing should be done for all dead/euthanized animals.

Semi-structured interviews, using the same topic guide as to assess feasibility (**Table 3.5**, *Appendix 6*) were analyzed to explain potential reasons for variation in fidelity between catchment areas. Questions relevant to assessing fidelity included asking participants: about their capacity/willingness to engage with others for IBCM activities; if they believed IBCM is part of their work; if they have confidence in their/colleagues' abilities to conduct IBCM; and if they have sufficient skills, training, resources, and support to implement IBCM.

LESSONS FOR ADAPTATION AND SCALE-UP

To facilitate the development of an updated ToC, three 2-hour workshops were conducted with key project stakeholders between March and May 2022. The aims of the study were identified by the research team and local stakeholders, then used to work backwards to determine the desired long- and short-term outcomes needed; the quantitative outputs directly resulting from the activities; what type of activities or intervention are required to reach those outputs and outcomes; and the resources and inputs needed to complete activities. These elements were comprehensively described in an updated ToC framework explaining how and why IBCM activities will guide and sustain rabies elimination efforts in the Philippines and how they are linked.

3.3.4 Data Analysis

Feasibility of IBCM Delivery

To assess the feasibility of IBCM delivery (Objective 1) in terms of acceptability and appropriateness, semi-structured interviews with PHWs and AHWs were thematically analyzed. Here, *acceptability* is defined as the perception among implementation stakeholders (i.e. PHWs and AHWs) that a given practice (i.e. IBCM) is agreeable, palatable, or satisfactory. Whereas *appropriateness* is defined as the perceived fit, relevance, or compatibility of the evidence-based practice (i.e. IBCM) for a given setting (i.e. Oriental Mindoro); and/or perceived fit of the practice to address a particular issue or problem (i.e. bite patient management and rabies surveillance) (Proctor *et al.*, 2011). Thematic analysis was conducted deductively using Normalization Process Theory (NPT) and inductively using descriptive codes, as described by Braune & Clarke (2006). NPT was chosen as the conceptual framework for analysis because it is designed for understanding and evaluating processes by which new health technologies and other complex interventions, such as IBCM, are routinely operationalized in everyday work and sustained in practice (May & Finch, 2009).

The PhD candidate developed the initial code framework, then along with three other project members (the team social scientist that conducted interviews, and two senior qualitative researchers), each independently applied the code to data (3 interviews) and amended the code frame over two iterations. The PhD candidate then applied this framework to all 28 interviews. Deductive codes used the four main constructs of the NPT framework: 1) Coherence, 2) Cognitive Participation, 3)

Collective Action, and 4) Reflexive Monitoring. The coded data were used to enhance and expand upon understanding of how IBCM operated during implementation and the factors that influenced the level at which activities were delivered. Barriers and facilitators identified were then compared to explain potential reasons for variation between catchment areas and participants (PHWs vs. AHWs). Analysis was done using NVivo 12 Pro qualitative data analysis software (QRS International Pty Ltd. NVivo Version 12, 2018).

Fidelity of IBCM Delivery

To understand the fidelity or extent to which IBCM was delivered according to initial protocols in terms of adoption/uptake (Objective 2), the IBCM database and semi-structured interviews were examined. Quantitative data indicators included: the number of PHWs and AHWs submitting data to the App; the percentage of completed risk assessments and animal investigations submitted to the App; and the number of samples collected for dead/euthanized biting animals. Calculations for these indicators are described in **Table 3.4**.

Qualitative data from semi-structured interviews were analyzed using the same NPT framework previously described to assess fidelity in terms of adoption. Here, *adoption* is defined as the intention, initial decision, or action to try or employ an innovation or practice (Proctor *et al.*, 2011). These data were used to expand on understanding the level of adherence and reasons for variation in the adoption of protocols.

Lessons for Adaptation and Scale-up

To assess how initial IBCM protocols and procedures were adapted to fit the local context (Objective 3), the initial and end-of-project Theories of Change were compared. These data were reviewed and summarized to identify how inputs, activities, outputs, outcomes, and aims changed over the course of implementation. Additionally, these data were appraised for internal accountability and to determine the extent to which project activities and outcomes were achieved. Notes were taken on how barriers were overcome, what facilitators promoted effective delivery, and why some catchment areas were more successful than others. Lessons for adaptation and scale up were then identified and incorporated into plans for future expansion to other provinces in the MIMAROPA region of the Philippines (2023-2026).

Ethics Statement

The study was approved by the Institutional Review Board of the Research Institute of Tropical Medicine in Manila, Philippines [IRB - 2019-02] and the College of Medical, Veterinary & Life Sciences Ethics Committee at the University of Glasgow (Ref No. 200210147). The participants recruited and interviewed provided their written informed consent to participate in this study.

3.4 Results

Phase 1: Pilot Study of IBCM Feasibility

IBCM App

During the 6-month feasibility study, it was immediately obvious that there were issues with the App, a key tool in the study design to establish data submission and communication channels. First, the risk assessment and animal investigation forms were not adequate according to the preferences of participants and stakeholders who requested they be made more similar to existing DOH paper-based forms. Second, technological difficulties prevented notifications (i.e. alerts) and data sharing between PHWs and AHWs via the App, both of which were primary functions described in initial IBCM protocols:

> *"PHW #11: If the App was functional, the MAOs would know right away if there was… say a dog bite incident in a certain barangay… and the victim's address, age, etc. [would be shared] and they would be alerted immediately…"*

While the project team was able to liaise with local stakeholders and participants to update the format of the App forms, the issues with the App's functionality were never rectified. This necessitated that the protocols for *Step 2: Triggering animal investigations* and *Step 4: Feedback and sharing results* (**Figure 3.4**) be updated to specify calling/texting or using the peer-support chat. While the peer-support chat was initially designed as a means for participants to interact and ask for guidance/feedback from each other and project stakeholders, it was adapted in Phase 1 into a channel for PHWs to report high-risk bites to their AHW counterparts for investigation.

IBCM Training & Materials

Training and materials were refined and tailored to the local context following the piloted training delivery in Southern Oriental Mindoro. Based on participant interviews, the pilot training was perceived as providing sufficient skills and knowledge to conduct IBCM activities. However, the project team and stakeholders noticed a lack of data submission and questions during interviews, observations, and interactions with participants that indicated confusion about the concept of IBCM and what their role was. Much of this confusion was due to technical issues with the App, making it infeasible for participants to implement IBCM according to initial protocols. Training materials were updated to reflect protocol adaptations regarding the App. Also, the protocols were updated to improve ease of interpretation and understanding by including visual tools and guidance, such as flow charts and hard copy manuals to be distributed to every ABTC and MAO in the province.

Phase 2: Evaluating Delivery of IBCM

Of the 57 PHWs and 38 AHWs who took part in at least one or more of the IBCM training sessions, 14 PHWs (24.6%) and 14 AHWs (36.8%) were interviewed. There were two refusals—one PHW and one AHW from different municipalities—with both stating they no longer wished to participate in the project due to busy workloads and other priorities.

Along with the NPT coding framework, several descriptive codes were identified as important in the semi-structured interviews. Descriptive themes identified, refined, and integrated into the four NPT constructs included: understanding and perceived value of IBCM (under Coherence); community participation and sustainability (under Cognitive Participation); integration into routine, training, capacity, support, IBCM App, animal investigations, risk assessments, resources, communication, and COVID-19/lockdown (under Collective Action). Other descriptive themes external to the NPT framework included: job responsibilities, request for support, mass dog vaccination/local ordinances, and PEP situation. Broadly speaking, the NPT constructs Coherence and Cognitive Participation were mostly used to describe acceptability and appropriateness; all four NPT constructs described barriers and facilitators to adoption, and variation in contextual factors; and Collective Action was used to describe the variability of fidelity/adherence to protocols between catchment areas.

3.4.1 Feasibility of IBCM Delivery

I. Acceptability and Appropriateness

PUBLIC HEALTH WORKERS

Most PHWs had a comprehensive understanding of IBCM (Coherence) as identifying which bites were high-risk vs. low-risk to inform PEP decisions and then reporting bite cases to their MAO counterpart. However, there was some confusion about the criteria to distinguish high-risk vs. low-risk bites. Some PHWs still used WHO categories of wound severity instead of the history of the biting animal to determine the risk of rabies. Others viewed IBCM as the program itself and/or felt the only difference between existing work and IBCM was the addition of data submission (the App vs. NaRIS):

> *"PHW #13: IBCM is an NGO? That addresses animal bites? That is where we learned the categorization of bite wounds from Category I to Category IV? Does it go up to four? Anyways, the goal is the eradication of rabies and to find the best strategy… for a rabies-free Mindoro… because I think Oriental Mindoro was one of the pilot sites of the program?"*

The majority of PHWs perceived IBCM as a valuable tool for better managing PEP and improving communication with the animal sector (Coherence) but struggled to integrate the extra workload into their routine (Collective Action). This indicates IBCM was highly acceptable to PHWs, but not appropriate for the setting. Some PHWs specifically questioned the value of entering data into the App since bite patient presentation to ABTCs was high and a full course of PEP is administered to patients regardless of the risk of exposure:

> *"PHW #11: Is it really necessary [to use the App]?... the people here, they really come to get vaccinated… some patients even when their bites are just Category I… even if we tell them that they don't need it because the [biting] dog is fully vaccinated… patients insist on getting their shots. People here are aware. They know about rabies, so they are afraid of contracting it."*

Trained PHWs were confident in their/colleagues' abilities to conduct IBCM activities (Collective Action), with many perceiving IBCM as not too different from their usual work practices (Coherence). While most believed they had sufficient training and skills for IBCM, they lacked human resources, particularly at the ABTCs with heavy patient loads (e.g. >80 bite patients per day).

ANIMAL HEALTH WORKERS

Most AHWs described IBCM as the investigation, management, and/or monitoring of potential rabies cases (Coherence). Others viewed IBCM as coordination between health and animal sectors; a tool to indicate emergency mass dog vaccination; or simply as sample collection for laboratory testing. One AHW described IBCM by the PHWs' role of assessing risk by WHO wound category.

The majority of AHWs perceived IBCM as a valuable intervention worth conducting for rabies control and were eager to have the skills, training, and resources necessary to implement IBCM:

> *"AHW #3: Yes, of course [there is value in doing IBCM]. We can monitor bite cases because of the connection between the MAO and the health sector and through our relationship with the Pro-Vet, unlike before, we would only find out about bites days after the incident… but now, if someone reports to the ABTC, they would call us, and we would be able to respond in a timely manner."*

While a few MAOs/AHWs conducted animal investigations prior to IBCM training, this was mostly a new job responsibility. Specifically, recording/encoding data, collection of samples, and use of RDTs were not done previously. Thus, although confident in their abilities to do IBCM in the future (Coherence), almost all AHWs strongly expressed the need for more in-person training sessions with demonstrations to improve their skills (Collective Action):

> *"AHW #15: IBCM is something we touch upon, but never fully practiced… because isn't IBCM the cooperation between our office and the RHU, and other concerned agencies? Based on the training, and also from my experience, we have yet to implement [IBCM] because our livestock coordinator is still requesting for actual training from [the project]... because we only had something like a webinar [online refresher training]? So that is all theoretical… we want to have the actual experience, [hands on] training on IBCM. That is why we have yet to put it into practice."*

Some AHWs had forgotten or never undergone training and/or noted they/colleagues were confused about the concept and their role with IBCM (i.e. believing all biting animals needed to be investigated or it was their responsibility to categorize the risk of the bite). Several trained AHWs had primary job responsibilities dealing with crops and little to no experience handling dogs. Many expressed concerns about their safety while handling potentially rabid dogs and being exposed. Others felt IBCM was useful, but not their area of expertise or responsibility unless assigned by their management (Cognitive Participation), indicating high acceptability, but low appropriateness:

> *"AHW #13: I think we lack knowledge… the proper training, because we were absent in at least one of the training sessions… it would be difficult to rush headlong into these [investigations] when we don't have the proper expertise. We wouldn't want to be responsible for… it's rabies… we are dealing with human lives here."*

II. Barriers and Facilitators to Implementation

BARRIERS TO DELIVERY

Limited capacity and resources

Both PHWs and AHWs were challenged by limited capacity, typically with only one person assigned per ABTC/MAO to complete the bulk of IBCM tasks. In addition to managing bite patients, PHWs were assigned to other programs such as immunizations, DOTS/TB, midwifery, oncology, vector-borne diseases, sanitation, and general community health services. Similarly, even though AHWs found IBCM to be valuable and wanted to participate in implementation, their current work responsibilities did not allow time for this:

> *"AHW #9: Sir, right now, with our current workload, we wouldn't be able to handle the added responsibility of IBCM. Our situation right now wouldn't really allow for it. But it would be very helpful especially with the number of deaths because of rabies - especially involving children."*

Most AHWs did not have work vehicles available to them and thus needed to use personal vehicles or pay for public transport to investigate animals. Only a handful of AHWs were able to claim reimbursement of expenses for fuel and travel. Both PHWs and AHWs frequently had limited or no internet connection and/or mobile reception to submit data to the App, with most needing to personally pay for mobile data to upload forms.

Technical issues and lack of One Health reporting

PHWs and AHWs faced barriers due to technical issues with the App including: compatibility with personal devices i.e. only available on Androids; inability to use/download the App; or losing password/username. Given that many participants did not use the App, there was insufficient data submitted to the IBCM database making it difficult for the project team to identify high-risk bites and suspected biting animals. Many AHWs relied on project staff to fulfill their role with IBCM:

> *"AHW #12: I spoke with a representative from the [district hospital] and we came to an agreement… they would report [bite cases] to me, and I would forward the info to [project team]... and if they can't go out to investigate, I would do it."*

A key barrier for AHWs was a lack of reporting from the health sector since they were reliant on this information to conduct investigations. Issues included: PHWs believing data encoded in the App was being sent to AHWs; PHWs not having MAO contact numbers, and PHWs/AHWs not being members of the peer-support chat. Some PHWs suggested it would be more feasible if bite patients or AHWs could initiate reporting by visiting the MAO or ABTC to check patient logbooks.

The COVID-19 pandemic/lockdowns were a barrier which severely diminished the level of in-person training, engagement, and presence the project team could have with participants for most of 2020 and 2021. During interviews, some PHWs and AHWs enquired as to whether the project was still ongoing; if their counterparts were still participating; and/or if they should continue following protocols and using the App.

FACILITATORS TO DELIVERY

High acceptability and willingness to adapt IBCM

Despite encountering barriers and complications during delivery, essentially all PHWs and AHWs perceived value and enthusiasm for IBCM and/or rabies control, agreeing that it was a major public health threat requiring prioritization and solutions. This high acceptability and advocacy of IBCM led some participants to take the initiative to adapt protocols to fit their local context. Participants were open to new ways of working and developed their own ideas for how to make IBCM work in their area, such as involving people external to the project:

> *"AHW #6: We had assistance from the barangay officials, we got all the information from them… we don't get info from the health center. We got our news from the barangay officials after they observed that the victim seemed to be going insane."*

Strong One Health rapport

Facilitators included a strong rapport or One Health link established previously to or resulting from IBCM. Municipalities that had a good relationship with their human or animal health sector counterparts had a major advantage in terms of the extent of communication/collaboration and initiating innovative adaptations to protocols:

> *“PHW #1: I talked with someone from the MAO and we agreed that if a bite victim comes in for treatment, we would send them to the MAO before they go get referred to the ABTC… so they can be interviewed and provide their contact details.”*

In addition, AHWs/MAOs that engaged with the community and had earned their trust had bite patients directly reporting to them and seeking advice. This helped facilitate coordination with the health sector, which often did not have time to report bite events to the animal health sector:

> *“AHW #11: [Bite victims] often come here for their shots… they think we also provide vaccines for humans, so we point them in the right direction to the ABTC… and we ask them ‘is the biting dog well-behaved now? Is it leashed? Is it vaccinated against rabies? When was the dog last vaccinated?’ That is what we usually do… and also get the name of the victim for validation, we coordinate with the health unit.”*

III. Variation in Feasibility due to Contextual Features

Variations in contextual features resulted in differing levels of IBCM feasibility between catchment areas. Prioritization of rabies control measures varied due to staff capacity, level of funding provided by LGUs, support from supervisors, number of competing priorities assigned to each ABTC/MAO, the enthusiasm of trained participants, and workload. ABTC staff at major hospitals were typically overburdened with high numbers of bite patient presentations. This often meant these PHWs were more experienced and confident in their abilities to manage bite patients and were able to more accurately assess the risk of bites, but it also left them with little to no time for encoding. However, larger hospitals that covered multiple municipalities had multiple MAOs they were required to coordinate with, challenging abilities to establish a rapport, and complicating follow-up and feedback of results. Out of the interviewed AHWs, only one had a veterinarian background, while the majority were heavily focused on crops, fisheries, and livestock. While most AHWs mentioned helping with annual MDVs, this was usually the extent of their rabies-related work. Municipalities closer in proximity to RADDL and the Pro-Vet office had a significant advantage in terms of transporting whole animals or samples for diagnostic testing.

3.4.2 Fidelity of IBCM Delivery (Adoption)

IBCM APP

Quantitative data from the project database showed that IBCM was not implemented as initially intended. Training and protocols stipulated that every participant should have the App downloaded on their phone or a tablet provided by the study to encode IBCM data. However, only 8 PHW usernames out of the 57 trained submitted risk assessments and 5 AHW usernames out of the 38 trained submitted animal investigations over the three years. This was largely due to a lack of interest in the App, experiencing technical difficulties (i.e. not being able to log in), and/or App incompatibility with their mobile device. Furthermore, at the time of the interview, over half of participants stated they did not have the App downloaded or, if downloaded, had never used it to submit IBCM data:

> *"PHW #15: We tried the App, but never got around to using it regularly. We don't have the App anymore - it got erased from my co-worker's phone, so we never used it to record cases. We were simply trained how to use it."*

RISK ASSESSMENTS

Risk assessments were not implemented according to IBCM protocols, as shown by the low percentage of completeness of data submitted to the App. Initial protocols stated that risk assessments should be performed for every bite patient presenting to ABTCs and submitted immediately (<24 hours). When compared to PHO records, risk assessments were completed for approximately 36.3% (11,501 of 31,654) of total bite presentations over the 3-year study: 43.3% in 2020 (3,623/ 8,370), 34.8% in 2021 (3,924/ 11,269), and 32.7% in 2022 (3,924/ 12,015).

Of the risk assessment data submitted 29.9% (3,435 of 11,501) was uploaded by hired project staff and 70.1% (8,066 or 11,501) by trained PHWs. However, more than 63% (5,107 of 8,066) of PHW-encoded data was completed by a single PHW (44.4% of all first-visit records) who, as a champion of the project, submitted almost complete records for their catchment area. Interview data and the database showed that the majority of bite patient records were submitted retrospectively, sometimes several months after the patient visited the ABTC.

ANIMAL INVESTIGATIONS

Animal investigations were also not implemented according to protocols as shown by the percentage of data completeness submitted to the App. Protocols specified that all bite patients deemed high-risk should trigger an animal investigation to be conducted and submitted to the App. Out of the 11,501 risk assessments performed over 3 years, 253 were assessed to be high-risk, and thus, required investigation. Over the 3-year period, records for 146 animal investigations were submitted to the App (**Figure 3.5**): 12 in 2020, 60 in 2021, and 74 in 2022. However, only 29.5% (43 of 146) of records were submitted by trained AHWs, while the rest were submitted by project staff after being given paper-based/oral reports from PHWs, AHWs, or local stakeholders. Moreover, upon review, many of the investigation data submitted were for biting animals that did not actually fit the high-risk criteria.

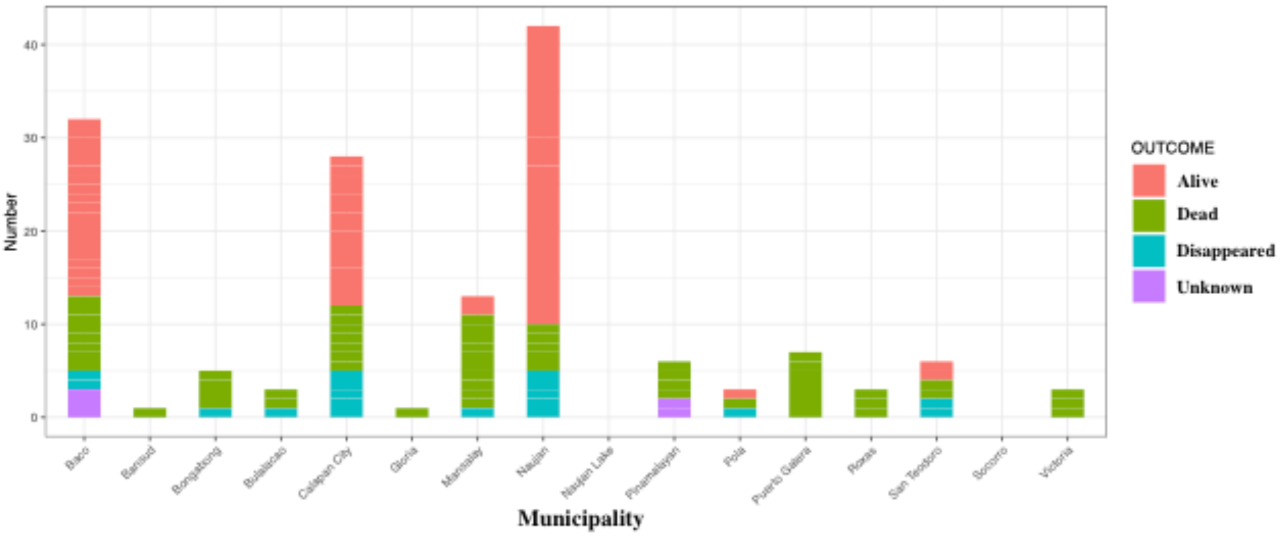


FIGURE 3.5 – SUMMARY OF ANIMAL INVESTIGATION OUTCOMES SUBMITTED TO THE APP FOR ORIENTAL MINDORO PROVINCE BY MUNICIPALITY. Four investigation outcomes were possible: 1) animal alive and healthy (pink), 2) animal dead/euthanized (green), 3) animal disappeared or not found (blue), and 4) animal unknown (purple).

Of the animal investigations submitted 56 recorded an outcome of “dead” indicating a sample should have been collected. Over the duration of the study, 28 samples were collected and submitted to RADDL for diagnostic testing using RDTs and confirmatory DFA testing. However, not all of these samples were directly linked to App-recorded investigation data. According to interviews, AHWs were often informed of high-risk animal bites too late, limiting their ability to observe the animal and collect accurate details of events and samples, if necessary.

VARIATION IN FIDELITY

There was noted variation to adherence between catchment areas in terms of both risk assessment and animal investigation submission. As shown in **Figure 3.6**, some ABTCs did not submit any data to the App during the entire three years, while others submitted intermittently with month-long gaps, and one continuously submitted all patient data throughout the project. This is similar to variation seen between MAOs, with some never conducting investigations or collecting samples to submit to RADDL for testing, and others proving high adherence to protocols via data and/or sample submission records. Variation in protocol adherence between the human and animal health sectors did not appear to influence one another or correlate (i.e. municipalities with high adhering ABTCs might have low adhering MAOs and vice versa).

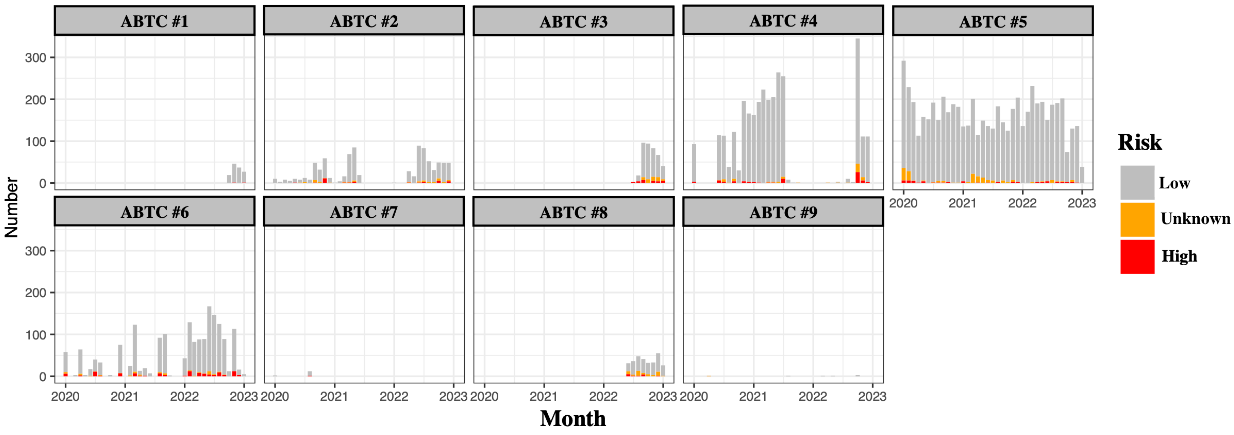


FIGURE 3.6 - TIME SERIES OF BITE PATIENT RISK ASSESSMENT DATA SUBMITTED TO THE APP FOR ORIENTAL MINDORO PROVINCE BY MONTH FROM DEC 2020 TO JAN 2022.

3.4.3 Adaptation and Scale-up

The process evaluation showed that while overall acceptability was high amongst participants, the intervention had limited appropriateness for the setting. There was limited uptake of IBCM due to barriers in the intervention design and implementation. IBCM training, protocols, and delivery were consistently adapted to the local context from the launch of the pilot study (2019) to the end of the project (2022). Participants, local stakeholders, and project staff identified several potential ways to improve upon participants' understanding/practice of IBCM, reduce barriers, utilize facilitators, and adapt protocols to the ongoing COVID-19 situation. Moreover, lessons learned from ABTCs and/or MAOS with high adherence were used as potential solutions to improve fidelity and delivery of IBCM in low-adhering catchment areas. Where possible, these adaptations were incorporated into IBCM protocols and procedures on a continuous basis throughout the study period. Over the course of the three-year study period, streamlining of protocols and delivery of IBCM improved in terms of reporting high-risk cases, One Health communication, engagement with the project team, and number of samples collected for testing.

ADAPTING TRAINING MATERIALS

- In 2020, IBCM field manuals with updated protocols were created as both online and hard copy resources distributed to each ABTC, RHU, and MAO within the province. These included laminated flow charts of steps involved in risk assessment and animal investigation protocols. During interviews, PHWs and AHWs stated these tools helped to address confusion about their role in delivering IBCM activities and provided easy-to-use guidance for decision-making processes.

- At the end of 2021, virtual training videos were developed with the inclusion of visual tools describing how to carry out IBCM protocols. This was launched as an online refresher training course via Zoom in January 2022. These online videos remained available as open-access resources to all participants, providing a means to train new staff and refresh the knowledge/skills of previously trained staff. In interviews, PHWs and AHWs noted how useful these videos were for addressing issues associated with high staff turnover and lack of recall of training/protocols.

ADAPTING THE ROLE OF PHW (RISK ASSESSMENTS)

- Around the end of 2021/beginning of 2022, a few ABTCs hired or assigned encoders specifically tasked to enter IBCM data. While this is not sustainable, it helped ABTCs catch up with retrospective data encoding from periods when the prioritization of COVID-19 activities prevented data submission for months.

- During the COVID-19 lockdowns, initial guidance requesting that PHWs submit risk assessments for first-time visits of every bite patient presenting to the ABTC was replaced by asking PHWs to prioritize submission of high-risk bite data. This promoted the improvement of real-time data submission of priority bite patients, allowing the project team to remotely identify high-risk cases through the IBCM database.

- Throughout the project, the team (e.g. the project coordinator/ Disease Surveillance Officers, DSOs) increasingly took a more proactive role in encoding data, contacting ABTCs to enquire about recent high-risk bites, and following up with bite patients/their families to obtain more details about the bite event to determine risk categorization. This improved the rapid identification of bite patients who may have been exposed to rabies.

ADAPTING THE TRIGGERING OF ANIMAL INVESTIGATIONS

- The peer-support chat was modified to be a primary method for reporting high-risk bites and trigger investigations, replacing the failed App function of automated alerts notifying of the need for investigation.

- Contact lists with MAO telephone numbers for each municipality were printed and distributed to every ABTC, providing an easier method to contact AHWs to trigger animal investigations.

- The project field staff (project coordinator/ DSOs) took a more proactive role reporting high-risk bites to the MAO to trigger animal investigations, addressing the issue of lack of reporting from PHWs/ABTCs.

ADAPTING THE ROLE OF AHW (ANIMAL INVESTIGATIONS)

- RADDL and project staff (DSOs/ project coordinator) were increasingly proactive in instructing MAO staff on protocols, guiding sample collection, conducting RDTs, investigating animals, submitting results to the App, and liaising feedback to stakeholders.

- RADDL staff facilitated AHW training for the project on safely handling and euthanizing animals, sample collection, in-field testing using RDTs, and transportation of samples to RADDL for confirmatory testing.

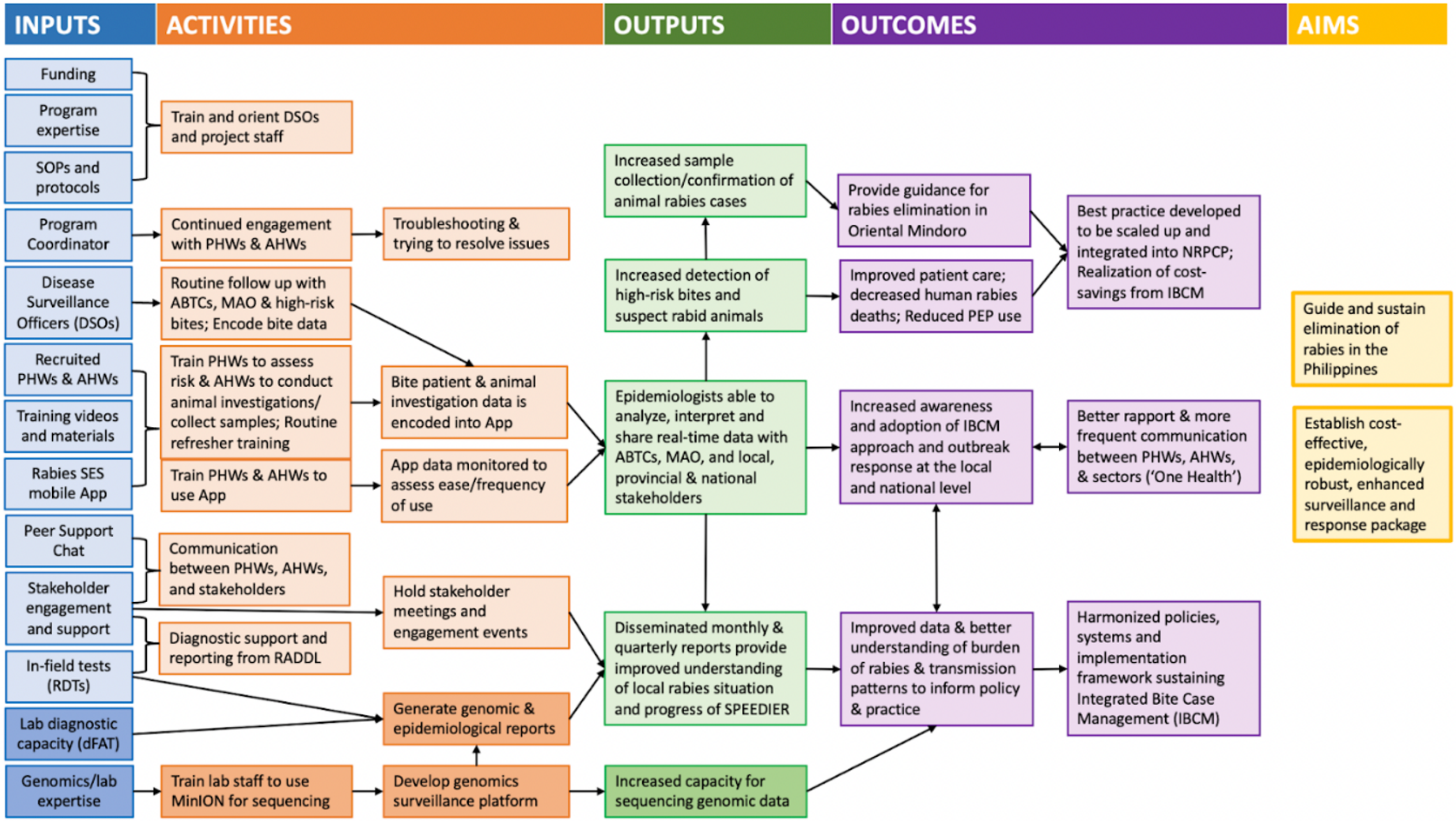
ADAPTING SHARING OR DATA/RESULTS

- Monthly reports were posted in the peer-support chats (one per subregion) to provide feedback to participants and local stakeholders. Reports showed and mapped the number of: high-risk bites reported, animal investigations conducted; and the total number of bite patient records submitted.

- The PHO, Pro-Vet, and RADDL stakeholders posted important updates in the peer-support chat to immediately notify participants.

3.4.4 Adapted Theory of Change

Workshops conducted with the core project team and local stakeholders to update the ToC showed that the aims of the IBCM intervention remained the same as stated in the initial ToC developed in 2019. Inputs, outputs, and outcomes underwent moderate adaptations. However, the most substantial changes were made to activities, which were simplified by removing ambitious and/or complex protocols not appropriate for the context. One major IBCM component removed from the protocols was the activity of using risk assessments to make PEP decisions, leading to the output that more appropriate PEP decisions would be made; and the outcome that this would result in indiscriminate PEP use, and thus costs, being significantly reduced. Additionally, the project team developed code to identify high-risk bite patients in the database, which was reported to and followed up on by the in-country project team. The role of the PHW and AHW were simplified by having project staff assist with encoding patient bite data to the App, following up on suspect animals, liaising with the team on the ground to investigate and collect samples, and reporting back rabies-related information. Activities and inputs were also updated to reflect the vital importance of project staff (i.e. the project coordinator and DSOs) in the delivery of IBCM. A revised ToC (**Figure 3.7**) was developed following these workshops to reflect overall adaptations and updates to protocols. In the updated ToC version, several assumptions were made about IBCM program theory, such as that IBCM activities would result in quantitative outputs, which would lead to behavior changes associated with the desired outcomes, and ultimately cause the achievement of the project aims.



ASSUMPTIONS

- IBCM training will lead to understanding of protocols at a proficient level to conduct IBCM activities, leading to accurate risk assessments, intersectoral collaboration, timely animal investigations, encoding of data, and sharing of feedback
- Communication and collaboration between sectors will facilitate rapport
- Improved epidemiological data will be used to guide and enhance rabies control measures, including mass dog vaccination

FIGURE 3.7 - REVISED THEORY OF CHANGE DEVELOPED BY CORE PROJECT TEAM AND LOCAL STAKEHOLDERS OVER THE COURSE OF THREE 2-HOUR WORKSHOPS FROM MARCH TO MAY 2022

3.5 Discussion

3.5.1 Key Findings

The process evaluation showed that protocols were initially not feasible for the effective delivery of IBCM in Oriental Mindoro province (Objective 1). While both PHWs and AHWs were enthusiastic about IBCM and perceived it to be a highly acceptable and valuable intervention, the original protocols were not appropriate for the setting due to barriers to implementation preventing the successful delivery of IBCM. The initial project design envisioned that following training a rapport would be established between human and animal health sector staff resulting in collaboration and communication to uptake IBCM practices. Instead, hired project staff and local stakeholders ended up conducting the majority of IBCM activities i.e. encoding data; following up on high-risk bite patients; liaising between participants, government offices, and sectors; and collecting animal samples and testing with RDTs.

Encountered barriers to implementation typically involved limited human capacity and resources; technical issues with the App; and lack of timely reporting between sectors. While COVID-19 complicated the delivery of IBCM and engagement with participants on the ground, there was evidence that initial protocols were infeasible even prior to the pandemic. Facilitators to implementation included high acceptability of IBCM; innovative adaptations to protocols; openness to new ways of working; and establishment of a strong One Health rapport. Training, particularly live demonstrations, which promoted confidence and empowerment was also an important facilitator, especially for PHWs and AHWs with less experience working with dogs and/or rabies. The extent to which barriers and facilitators influenced the feasibility of IBCM delivery varied substantially between catchment areas. Some municipalities experienced success on the human health side but failed to uptake IBCM on the animal health side or vice versa.

IBCM was not implemented as initially intended by protocols as shown by the limited extent of adoption of IBCM practices by participants (Objective 2). Completeness of quantitative data submitted to the IBCM database revealed that only 8 PHWs of 57 trained and 5 AHWs out of 38 trained were submitting data via the App. At the time of interviews, over half of the participants, particularly AHWs, stated they did not have the App downloaded or had never used the App. Many PHWs trained to perform risk assessments did not encode bite patient data into the App or communicate with their AHW/MAO counterparts according to initial protocols. Without receiving information about suspected biting animals from PHWS, the AHWs were often unaware of required investigations. Yet, even if informed, oftentimes AHWs did not conduct investigations or report results in the App as stated in the protocols.

Protocols and delivery of IBCM were adapted to the local context from the beginning of the project (2019) to the end (2022) (Objective 3). Adaptations differed between catchment areas with varying levels of success. Tasks initially designated to be completed by PHWs and AHWs, such as encoding bite patient data and triggering/conducting investigations, ended up being conducted by project staff (the project coordinator and DSOs). In addition, refresher training was required following the pandemic which included open-access online video resources which participants found to be useful. Adaptations improved the feasibility and fidelity of IBCM practices over the 3-year study. By the end of 2022, there was an obvious improvement in the success of IBCM as shown by an increase in reporting, number of animal investigations conducted, and number of detected animal cases.

3.5.2 Limitations

The IBCM implementation study began a few months prior to the COVID-19 pandemic and subsequent lockdowns in the Philippines, which immensely affected peoples' routines, ways of working, and priorities. Specific to rabies, recent research has shown the major impact the pandemic had on practices associated with control programs globally (Nadal *et al.*, 2022; Gongal *et al.*, 2022). This limited the scope of our analyses, since this process evaluation was designed using an NPT framework to investigate the extent to which IBCM practices were routinely implemented, embedded, and integrated into social contexts (May & Finch, 2009). Moreover, the protocols and context changed to adapt to situations unique to each catchment area and/or municipality over the study duration. While efforts were made to document this, there were still gaps in the data collected as researchers were unable to visit and engage with participants directly due to local travel restrictions.

While interviews were consistently conducted no more than 1-2 months following the training, the timeline of data collection spanned the entire 3 years of the study which likely influenced the results. This meant that only one point in time was captured for each individual and sector per municipality. It is also likely that variation in the local context fluctuated between catchment areas during the study in terms of the resources available; COVID-19 restrictions; level of training, skills, and confidence; and assigned workload/priorities. Furthermore, the refusals to participate in interviews that were encountered may have biased data towards PHWs and AHWs with a more positive outlook/enthusiasm for the project. Lastly, sometimes the person interviewed was not the primary individual responsible for conducting IBCM activities, limiting their experience and perspective of the extent to which IBCM was being delivered as stated in the protocols.

3.5.3 Wider Context

The wider benefits of implementing IBCM in the Philippines have been previously demonstrated in case studies in the provinces of Bohol and Albay, concluding IBCM is imperative to achieving and maintaining freedom from rabies (Rysava *et al.*, 2019; Rysava *et al.*, 2022). Both studies were able to successfully implement IBCM over a 12-13 month period, enhancing surveillance and showing that >90% of bite patients receiving PEP from ABTCs were bitten by healthy animals that posed zero risk of rabies. Substantial evidence points to recommendations that IBCM could support the Philippines to reduce expenditure on PEP by at least half; guide control measures to reach elimination; and provide sensitive surveillance for real-time monitoring to rapidly detect incursions and interrupt localized outbreaks. However, despite IBCM's proven effectiveness in many settings around the world, implementing an effective and sustainable IBCM system has proved challenging in the Philippines due, in part, to its decentralized government spanning over 7,000 islands. This far, all IBCM case studies in the Philippines were implemented by small groups of externally hired staff (i.e. not government employees) and none have been sustainably integrated into policy at the local-level.

This presumably is the first implementation study of IBCM in the Philippines, and potentially one of the first in the world. It is also the first instance where IBCM is being implemented in the Philippines using a trained existing government workforce, as opposed to hired project staff. Currently, no other research has been published on tailoring IBCM guidance to the local context to improve routine uptake, integration, and sustainability of practices. To successfully integrate IBCM protocols as a part of NRPCP guidelines, a best practice needs to be developed and adapted for scale-up nationwide. This means that IBCM procedures will likely need to be adaptable to fit the varying contextual features of each locality (Swedberg *et al.*, 2022). Both epidemiological and non-epidemiological features will need to be considered when developing protocols to account for local variation in rabies endemicity (e.g. declared free vs. endemic), socio-economic status, health-seeking behaviors, resources available, beliefs, attitudes, practices, geography (urban vs. rural), financial situation, and government structure (Hawe *et al.*, 2015).

3.5.4 Conclusions & Recommendations

Overall, the findings from this study lead to several key recommendations for scaling up IBCM in the Philippines. First, it is unsustainable to request additional work be performed without compensation, particularly when it duplicates job responsibilities i.e. submission of bite patient records to NaRIS and an App. Second, human and animal health sectors are already burdened with heavy workloads and priorities other than rabies, thus IBCM protocols need to reduce or ease work to streamline activities to avoid wasting time and resources. To integrate IBCM practices into routine work, surveillance tools such as the App and IBCM database need to be incorporated into existing national surveillance systems (e.g. NaRIS, PIDSR, Phil-AHIS). Third, IBCM protocols must be advocated by national and provincial government guidelines to improve the feasibility and likelihood of integration and sustainability of practices. This is true not only to achieve enhanced surveillance but also to promote health workers' ability to make risk-based PEP decisions to support more judicious PEP administration. Health workers are currently not willing to risk liability for withholding PEP from patients bitten by healthy vaccinated animals, unless mandated by national guidelines.

CHAPTER 4

Using Integrated Bite Case Management to estimate the burden of rabies and assess surveillance performance in Oriental Mindoro, Philippines

4.1 Abstract

Despite national efforts for elimination, dog-mediated rabies remains endemic in the Philippines. The widespread establishment of Animal Bite Treatment Centers (ABTCs) with free provision of post-exposure prophylaxis (PEP) has improved accessibility. Yet, the incidence of healthy bite patients seeking PEP has increased unsustainably. Meanwhile, dog vaccination coverage is inadequate for controlling rabies and current surveillance is ineffective. Over 3 years, enhanced rabies surveillance data was collected using Integrated Bite Case Management (IBCM) in Oriental Mindoro province. Adapting a probabilistic decision tree model, the burden of rabies was estimated, surveillance performance was evaluated, and the impact of rabies prevention practices was assessed. The incidence of bite patients receiving PEP was high (1,160/100,000 persons/year), with <2% deemed high-risk for rabies exposure (<25/100,000 persons/year). Although this might suggest high health-seeking behavior, this study found that an average of just 71.4% of probable rabies-exposed patients seek PEP. Routine surveillance confirmed <1% of circulating animal rabies cases, whereas IBCM resulted in a fivefold increase in case detection. This model suggests that between 275-838 dogs develop rabies annually in Oriental Mindoro, equating to 3-5 per 1,000 dogs/year. On average, 18-28 human deaths and 668-1,039 DALYs were averted by PEP each year at a total cost of >$535,385 USD per year, i.e. $23,110 and $634 USD per death/DALY averted. These results highlight that current PEP practices are acceptable in terms of preventing rabies deaths but are inefficient in terms of cost-effectiveness without using risk assessments to determine the risk of rabies exposure. In conclusion integrating an IBCM approach into national policy, if implemented effectively, has the potential to guide PEP

administration, thereby reducing unnecessary expenditure on PEP and informing control of rabies through mass dog vaccination.

4.2 Introduction

Rabies is a viral zoonotic disease which is nearly 100% fatal without prompt administration of post-exposure prophylaxis (PEP) to prevent infection (WHO TRS, 2018). Practically all the estimated 59,000 human rabies deaths that occur annually are transmitted from bites from domestic dogs in low- and middle-income countries across Africa and Asia (Hampson *et al.*, 2015; WHO Rabies Modelling Consortium, 2019). Similar to other neglected diseases, only a small percentage of human rabies deaths and animal rabies cases are reported in official national and international surveillance statistics. This assumed underreporting of human and animal cases is largely due to ineffective and unreliable passive surveillance in endemic countries, leading to reduced advocacy, funding, and engagement (Taylor *et al.*, 2017; Wallace *et al.*, 2015). Implementing methods to enhance case detection is imperative to inform and evaluate effective rabies control.

In the Philippines, dog rabies was first confirmed in 1910 when a human case was reported and Negri bodies were found in the brain of the biting dog (Cruz, 2019). Since then, various control initiatives have been led by the government, attempting to eliminate rabies from the country. In 2007, the National Rabies Prevention and Control Program (NRPCP) was mandated by the Anti-Rabies Act (Republic Act No. 9482), including the widespread establishment of Animal Bite Treatment Centers (ABTCs) to provision free PEP to bite patients (NRPCP MOP, 2019). Though this policy has improved access, the number of bite patients seeking PEP has increased almost sevenfold from its introduction in 2007 (~197 per 100,000 persons/year) compared to the last 7 years (>1,030 per 100,000 persons/year) (NRPCP Strategic Plan, 2020). Moreover, dog-mediated rabies remains endemic in most of the Philippines and the reduction in mortality has plateaued to around 200-300 deaths reported annually. Though, due to insufficient surveillance the actual number of deaths is likely higher.

Integrated Bite Case Management (IBCM)—a One Health approach to implementing cost-effective rabies surveillance—is recommended by WHO and partners as part of the global strategic plan to end human deaths from dog-mediated rabies by 2030 (*Zero by 30*) (Zero by 30, 2018; Undurraga *et al.*, 2017; Franka & Wallace, 2018). The One Health approach recognizes the interconnections between the health of humans, animals, and their shared environment (FAO, UNEP & WHO, 2022). Case studies using IBCM have previously been implemented in the Philippines on the island of Bohol (Rysava *et al.*, 2019) and in Albay Province (Rysava *et al.*, 2022). This approach uses bite patient risk assessments to identify bites from suspected rabid animals which should then be investigated, and samples collected for confirmation. IBCM has the potential to enhance surveillance enabling better estimations of the true burden of rabies; evaluation of control and prevention measures; informing of PEP administration with the potential to reduce unnecessary use of PEP; advocacy for funding and engagement; and guidance on the implementation of the national rabies program (Swedberg *et al.*, 2022).

Here, an adapted decision tree framework was used (Cleaveland *et al.*, 2002; Hampson *et al.*, 2015; Rajeev *et al.*, 2019) to better understand the burden of rabies and evaluate prevention and control measures in the Philippines. The objectives of this study were to 1) more accurately estimate the burden of rabies in the province of Oriental Mindoro; 2) evaluate the performance of surveillance systems currently in place, and 3) analyze the economic costs and benefits of PEP policies, extrapolating across the Philippines. This study aims to determine the value of integrating an intersectoral surveillance system, such as IBCM, into national policy to support the Philippines in achieving rabies freedom by 2030.

4.3 Methods

A 3-year (2019-22) implementation study of IBCM beginning in January 2020 to December 2022 was established in Oriental Mindoro province, Region IV-B, MIMAROPA, Philippines. SPEEDIER (Surveillance integrating Phylogenetics and Epidemiology for Elimination of Disease: Evaluation of Rabies Control in the Philippines) aimed to deliver a cost-effective, epidemiologically robust, enhanced surveillance and response package to guide and sustain the elimination of rabies from the Philippines. Methods previously used in studies conducted by Cleaveland *et al.* (2002), then later by Hampson *et al.* (2015) and Rajeev *et al.* (2019) were adapted for this study. Using this adapted decision tree framework, I estimated the annual number of rabid animals, human rabies exposures, human deaths and disability-adjusted life years (DALYs) averted, the cost per human rabies death/DALY averted, and the probability of seeking PEP. The framework used aggregate government epidemiologic and demographic data, enhanced surveillance data collected through IBCM, and parameter values derived from the literature. Model estimates were then used to evaluate the current surveillance performance and cost-effectiveness of PEP policies for the province, which were extrapolated to the Philippines. Data analysis and figures were completed using the R programming language (version 4.2.1, 2022).

4.3.1 Study Site

Canine rabies is endemic throughout the province of Oriental Mindoro (**Figure 4.1**), which comprises 15 municipalities and a human population of 908,339 (PSA Census, 2020). As of 2022, there were nine health facilities with accredited ABTCs administering PEP and nine Rural Health Units (RHU), without ABTCs, providing wound care and then referring patients for PEP. Of the nine ABTCs, three are major hospitals where the majority of bite patients are present, while the remaining six are smaller community-level clinics with lower patient volumes. This network of ABTCs/RHUs spanning the province acted as a valuable sentinel for collecting rabies surveillance data through IBCM.

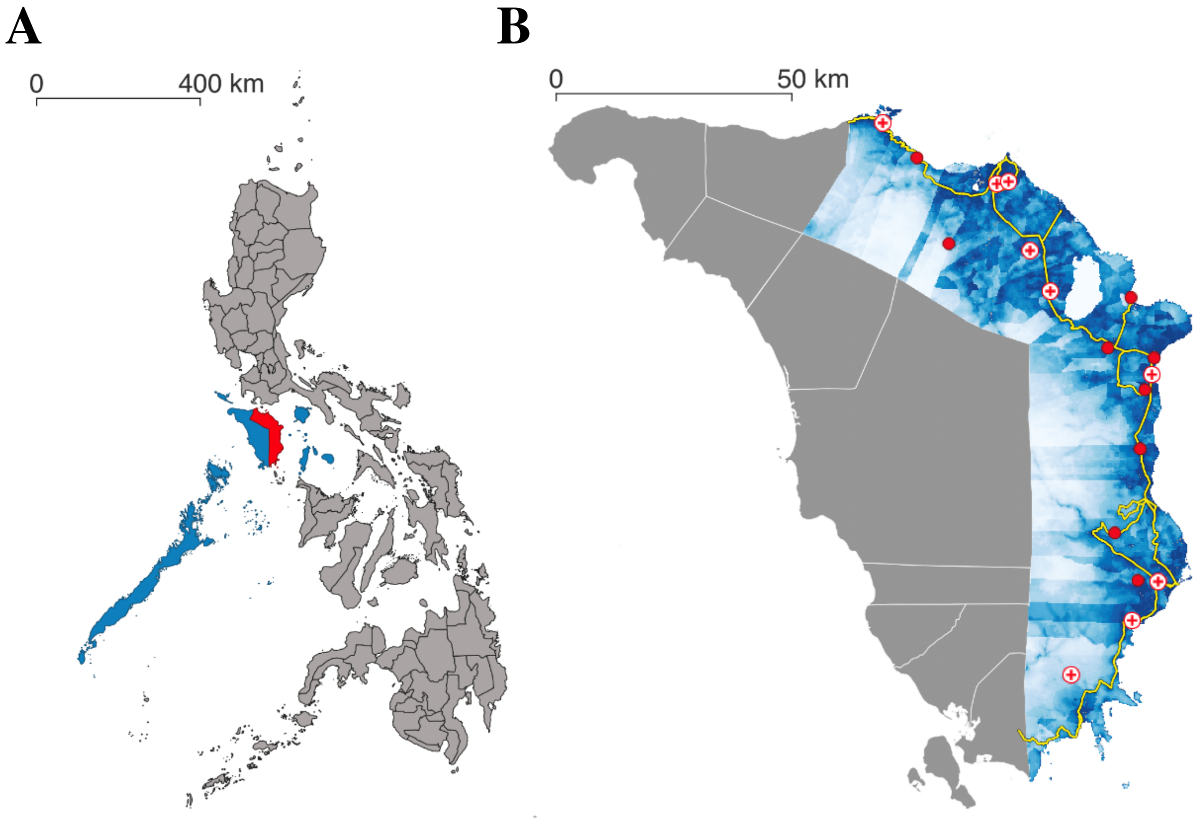


Figure 4.1 - Location of the province of Oriental Mindoro, Philippines. (A) Philippines provinces showing MIMAROPA region (blue) including Oriental Mindoro (red). (B) Oriental Mindoro Province on the island of Mindoro, showing the human population density (blue), major primary roads (yellow), and the nine Animal Bite Treatment Centers (red crosses) and nine Rural Health Units (red dots) without ABTCs that refer bite patients for PEP. Human density was calculated at the barangay-level from 2020 census data (PSA Census, 2020). Polygon and polyline data were sourced from UN-OCHA Humanitarian Data Exchange Project (UN OCHA, 2020). Gray shaded area is the adjacent province of Occidental Mindoro and its municipalities.

Throughout the province, PEP is administered following the 4-dose Thai Red Cross intradermal (ID) regimen (day 0, 3, 7 and 28) (Khawplod *et al.*, 2006). A 0.5mL vial (Speeda, China) typically provides four 0.1mL ID doses with wastage of the last 0.1mL. Considering each patient receives two 0.1mL ID injections per visit, this equates to ~2 vaccine vials per patient for a course. Recently updated protocols in the province specify ERIG should be given primarily to WHO Category III bites on the first visit, with 1 vial per patient provided for free and any additional vials required to be purchased by the patient. Typically, any bite victim presenting to the clinic will receive PEP regardless of their risk of rabies (i.e. including Category I non-exposure events from a healthy vaccinated animal). In rare occurrences of PEP stockouts, ABTC nurses use a more risk-based approach to PEP administration, saving the free PEP supply for more severe Category II and III bites.

In each municipality, there is a Municipal Agriculture Office (MAO) responsible for crops, livestock and, to a lesser extent, zoonotic diseases, such as rabies. The MAO, in coordination with the Provincial Veterinary Office (Pro-Vet), conducts intermittent dog vaccination campaigns. However, achieved coverage is heavily reliant on the allocated budget and thus varies significantly between municipalities. Furthermore, most dog vaccination campaigns were canceled in 2020 and 2021 due to the COVID-19 pandemic. Just south of the capital, Calapan, is the location of the Regional Animal Disease Diagnostic Laboratory (RADDL) for the MIMAROPA region, which consists of five provinces: Occidental Mindoro, Oriental Mindoro, Marinduque, Romblon and Palawan.

4.3.2 Data Collection

Aggregate Government Records

Human population data from the 2020 government census (PSA Census, 2020) for Oriental Mindoro and its 15 municipalities were used to estimate the dog population, and denominators for bite patient and rabies exposure incidence. Laboratory diagnostic data for animal samples tested for rabies from RADDL—both direct fluorescent antibody test (DFA) and lateral flow device (LFD)—were used to evaluate surveillance performance. When RADDL was unable to complete diagnostic testing (e.g. lack of working fluorescent microscope or broken storage freezer), LFD testing was conducted, and then samples were sent to the Research Institute for Tropical Medicine (RITM), located outside of Manila, for confirmatory testing with DFA. All diagnostic test results for samples from Oriental Mindoro were consolidated in RADDL records.

To summarize bite patient characteristics, Provincial Health Office (PHO) quarterly and annual reports compiled from ABTC patient logbooks were used. These records, collected since 2007 for the National Rabies Information System (NaRIS), include patient data such as demographics, wound location, WHO exposure category, species of biting animal, and PEP administration and compliance (DOH NaRIS, 2007). These data were used to estimate the incidence of bite patient presentations; for prospective comparison with IBCM data to determine the completeness of risk assessments performed (numerator) over total bite patients visiting ABTCs (denominator); and for subsequent extrapolation. Reports from investigations of human deaths by the PHO were used to summarize the date, location, and circumstances of human rabies cases from 2020-2022.

Lastly, PHO budget/procurement reports were used for inputs related to PEP costs, including average doses/vials per bite patient, and to determine the frequency of use of equine rabies immunoglobulin (ERIG). When estimating the cost of PEP per patient and per death/DALY averted, the costs of both human rabies vaccine and ERIG were included. Cost estimates and evaluation of cost-effectiveness did not account for PEP administration costs (e.g. personnel, syringes, etc.). When extrapolating cost estimations for the Philippines, NRPCP records were used for the average number of bite patients presenting to ABTCs and Department of Health (DOH) national human rabies death records (NRPCP Strategic Plan, 2020).

IBCM Data

IBCM data were collected over 3 years (Jan 2020-Dec 2022) as a part of SPEEDIER. The study involved training ABTC nurses to perform risk assessments for patients seeking care following a bite/exposure event. In addition to government-required data (for NaRIS), nurses were asked to record information about the biting animal (e.g. health/vaccination status, owned/not owned, alive/dead) and circumstances of the bite. This information was submitted via a standardized form through a bespoke mobile phone-based application previously developed for IBCM in Tanzania then adapted for the context in the Philippines (Lushasi *et al.*, 2020). Data submitted to the IBCM database for this study were not integrated into NRPCP records.

IBCM protocols specified that if the biting animal was suspicious for rabies, the nurse should trigger an investigation by contacting their designated animal health counterpart (SPEEDIER Study Protocols v9, 24 June 2022). While initial protocols also stipulated that PEP decisions should be based on the risk category, this was never implemented and PEP provisioning continued to follow DOH protocols, typically being provided indiscriminately to all bite patients. Animal health workers were trained to conduct animal investigations and record data on the suspected animal, following up for the 14-day observation period, and collecting brain samples for diagnostic testing if the animal was dead/euthanized. LFDs (BioNote: sensitivity of 0.95 and specificity of 1.00) (Kimitsuki *et al.,* 2020) were provided to animal health workers and RADDL staff for in-field and laboratory-based testing of samples. Animal cases were confirmed either at RADDL or RITM with DFA, one of several gold-standard tests recommended by WHO (WHO, Rupprecht, Fooks & Abela-Ridder, 2018).

While initial protocols intended to use animal investigation data to retrospectively update patient risk categories from investigations of biting animals, these data were not consistently collected due to restrictions from the COVID-19 pandemic. Thus, for this study, patients were classified as either low-risk, unknown-risk, or high-risk for rabies exposure based on the patient risk assessment from their first visit to the ABTC, with the exception of laboratory-confirmed biting animals, for whom risk categories were updated retrospectively. The risk of exposure categories used in this study are based on the following WHO animal case definitions (WHO TRS, 2018):

- **Low-risk:** (WHO definition "Not a case") - Biting animal had no clinical signs of rabies and was healthy and alive 14 days after the bite/exposure event or tested negative for rabies (if euthanized/killed)
- **Unknown-risk:** (WHO definition "suspected" or "probable") **-** Biting animal not identified or found; therefore, the history of the animal was unknown (e.g. vaccination/health status, contact with suspected, probable, or confirmed rabid animal, health status, etc.)

- **High-risk**: (WHO definition "suspected", "probable" or "confirmed" animal case) - Biting animal showed clinical signs of rabies (e.g. aggressive/erratic behavior, hypersalivation, paralysis, tremors, abnormal vocalization, loss of appetite); had history of contact with suspect/confirmed rabid animal; and died within 14 days of exposure event; or tested positive for rabies

4.3.3 Data Analysis

Decision Tree Model

A decision tree framework was used to probabilistically describe the steps by which rabies infection in dogs leads to human exposures and deaths, and associated costs. This type of framework has been used previously to estimate the burden of rabies (Cleaveland *et al.*, 2002; Rajeev *et al.*, 2019). Here, the framework was extended to utilize IBCM data and further estimate surveillance performance and cost-effectiveness of prevention measures.

A few assumptions were made to simplify this analysis. It was assumed that all bite patients who reported to an ABTC received PEP, considering that shortages and vaccine refusal are rare in Oriental Mindoro and that reported human deaths from rabies were recorded correctly with a high probability ($P_{obs|death}$). Study estimates and 95% prediction intervals (PrI) were based on 1000 probabilistic draws of parameters described in **Table 4.1**, following the decision tree framework.

IBCM risk assessment classifications were used to assign patients as either bitten by healthy dogs (low-risk) or rabid dogs (high-risk), with uncertainty based on the observed variation in IBCM risk assessments (lower limits included high-risk only, while the upper limit included high-risk + unknown-risk). To account for incomplete IBCM data, the proportion of high-risk bites was extrapolated using complete records from one ABTC, a major hospital accounting for over half of total IBCM records, to the rest of the province and used the resulting estimates in the decision tree model.

Total exposures were calculated as the sum of high-risk exposures, assigned prospectively, that sought PEP (from IBCM data) and estimated exposures that did not seek PEP extrapolated from recorded human rabies deaths. Similarly, numbers of rabid dogs were estimated from total exposures and the average number of people bitten per rabid dog, $P_{\text{bites|rabid\_dog}}$. Details of these extrapolations are described below and outlined in **Figure 4.2**.

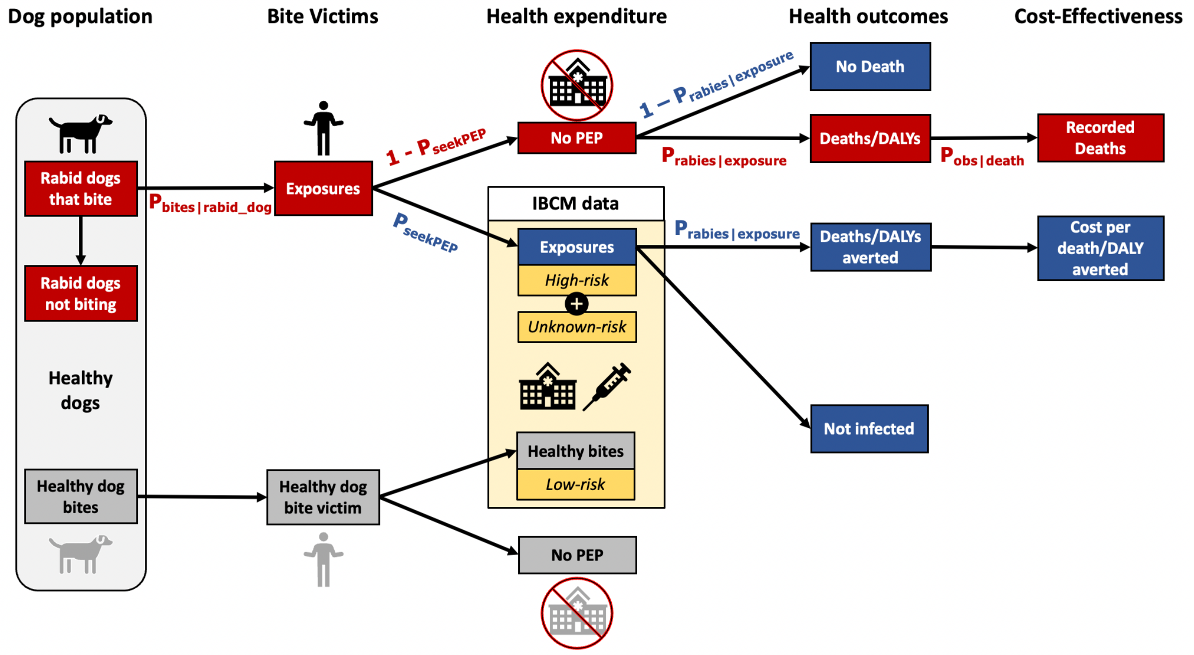


Figure 4.2 - Adapted decision tree to estimate burden of rabies and deaths averted by PEP. This framework illustrates the steps taken in the decision tree model to probabilistically estimate outcomes associated with rabies infections in dogs and resulting human exposures and deaths. IBCM data inputs are shown in yellow boxes. High-risk events are shown in red boxes. Low-risk events are shown in blue boxes. Healthy dog bite data not used in model estimates are shown in gray boxes.

Parameter Estimates

Parameters for the decision tree modeling used government or IBCM data from the Philippines to reflect local context where possible (**Table 4.1 and 4.2**). When national or regionally specific data were not available, probabilities from the literature were used, including $P_{rabies|exposure}$ and $P_{bites|rabid\_dog}$ calculated from contact tracing data from Tanzania (Changalucha *et al.*, 2019; Hampson *et al.*, 2016).

The probability of rabies-exposed bite victims seeking PEP ($P_{seekPEP}$) was estimated from the probability of developing rabies in the absence of PEP ($P_{rabies|exposure}$), IBCM risk assessments, and observed rabies deaths ($D_{observed}$). Here, it was assumed deaths were observed with high probability ($P_{obs|death}$):

$$D_{Total} = D_{observed} / P_{obs|death}$$

To estimate total exposures (E_{Total}), estimates of exposures who did not seek PEP (E_{no_PEP}) were summed with exposures who did (E_{PEP}) derived from the IBCM risk assessment data.

$$E_{no\_PEP} = D_{Total} / P_{rabies|exposure} \qquad E_{Total} = (D_{Total} / P_{rabies|exposure}) + E_{PEP}$$

$P_{seekPEP}$ was calculated from the estimates of total exposures and exposures that did not seek PEP ($P_{seek} = E_{no\_PEP} / E_{Total}$), while deaths averted ($D_{averted}$) were estimated from rabies-exposed patients who sought PEP and the probability of developing rabies: $D_{averted} = E_{PEP} \times P_{rabies|exposure}$.

Annual PEP costs were calculated by adding total human rabies vaccine and ERIG costs per year ($C_{Total} = C_{HRV} + C_{ERIG}$), using PHO records for the number of bite patients receiving vaccine (T_{HRV}) and ERIG (T_{ERIG}) and cost variables detailed in **Table 4.2.** When extrapolating across the Philippines, NaRIS records for number of bite patients receiving PEP were used.

$$C_{HRV} = T_{HRV} \times ID_{Avg} \times ID_{Cost} \qquad C_{ERIG} = T_{ERIG} \times ERIG_{Avg} \times ERIG_{Cost}$$

The average cost per death averted was estimated as total annual PEP costs divided by estimated deaths averted ($C_{Death} = C_{Total} / D_{averted}$). Similarly, the average cost per DALY averted was estimated by dividing total PEP costs by estimated DALYs averted ($C_{DALY} = C_{Total} / DALY_{averted}$).

DALYs were calculated according to methods developed by WHO, by adding Years of Life Lost (YLL) and Years of Life lived with Disability (YLD). Estimates for YLL used an average life expectancy in the Philippines of 72.12 years (Work Bank, 2020) and the average age of deaths recorded in Oriental Mindoro province during the 3-year study period (35 years). For rabies, YLD are considered insignificant due to the acute and fatal nature of rabies, and therefore were not included in DALY estimates.

Definition	**Parameter**	**Distribution/ Data**	**Point estimate/ range for main model**	**Range for sensitivity analyses**	**Source**
Probability of developing rabies after exposure in the absence of PEP	$P_{rabies\|exposure}$	Binomial	0.165	0.133 - 0.201	Changalucha *et al*., 2019
Average number of persons bitten per rabid dog	$P_{bites\|rabid\_dog}$	Negative Binomial	Mu = 0.3862 Size = 0.7055	0.15 - 0.50 NA	Hampson *et al*., 2016 Ferguson *et al., 2023*
Probability of human rabies death being observed and recorded in official records	$P_{obs\|death}$	Binomial	0. 90	0.5 - 1.0	Assumption, based on discussion with stakeholders
Rabies exposures seeking care and receiving PEP	E_{PEP}	IBCM	High-risk bite patients - (high-risk + unknown-risk)	0.5 * high-risk bite patients - high-risk + unknown risk bite patients	IBCM data (see text for details)
Human:dog ratio for Oriental Mindoro	HDR	Uniform	3-10	3 - 10	PSA Census, 2020; Chaudhari *et al*., 2022; Dizon *et al.*, 2022

TABLE 4.1 - PARAMETERS AND DATA USED IN THE DECISION TREE MODEL.

Definition	Parameter	PEP Cost Variables	Source
Average number of vaccine vials per patient (0.5 ml ARV Speeda)	NA	~ 2	Oriental Mindoro PHO bite patient, budget, and financial records
Average cost of 1 vaccine vial (0.5 ml ARV Speeda)	NA	$25 USD	
Average number of ID injections per patient	ID_{Avg}	~ 6	
Cost of 1 ID injection of vaccine	ID_{Cost}	$6.25 USD	
Cost of vial of ERIG (5 ml EQUIRAB)	$ERIG_{Cost}$	$45 USD	
ERIG dosage per 5 ml vial	NA	1 vial / 25 kg	
Average number of ERIG vials per patient	$ERIG_{Avg}$	~ 2	Rysava *et al.*, 2022

TABLE 4.2 - COST VARIABLES RELATING TO PEP PROVISIONING. ERIG = equine rabies immunoglobulin. ABTC = Animal Bite Treatment Center. PHO = Provincial Health Office.

Sensitivity Analysis

A sensitivity analyses was conducted comparing model estimates of human deaths, total exposures, $P_{seekPEP}$, rabid dogs and deaths averted across a range of uncertainty to examine the influence of specified parameter values. For the probabilistic sensitivity analysis, 1000 draws were taken across a uniform distribution of the ranges specified in **Table 4.1** for each of the following: HDR, E_{PEP}, human deaths, $P_{obs|death}$, $P_{rabies|exposure}$ and $P_{bites|rabid\_dog}$. Some variables (e.g. HDR) had high uncertainty in the baseline analysis and remained unchanged for the sensitivity analyses.

Ethics Statement

Ethical approval for the study was obtained from the Research Institute for Tropical Medicine (RITM), Department of Health (2019-023) and the University of Glasgow, College of Medical, Veterinary & Life Sciences Ethics Committee (Ref No. 200190123).

4.4 Results

4.4.1 Characteristics of Bite Patients

Between January 2020 and December 2022, a total of 31,654 bite patients presented to ABTCs in Oriental Mindoro to receive PEP for animal bites/exposures. This equates to an average of 10,550 (min=8,370, max=12,015) patients per year, 880 patients per month (min=688, max=1,133), and an incidence of 1,160 bite patient presentations per 100,000 people annually.

Characteristics of bite patients recorded in ABTC clinic registers are described in **Table 4.3**, including data from the year prior to when IBCM started (2019) for comparison before the COVID-19 pandemic.

Year	**2019**	**2020**	**2021**	**2022**	**4 Year average**
Recorded human deaths	5	9	7	9	8
Total bite patients	9217	8370	11269	12015	10218
Mean patients per month	768	698	939	1001	852
Bite incidence (per 100,000)	1015	921	1241	1323	1125
Percentage male	49.5	49.9	48.2	47.6	48.7
Bites under 15 yrs (%)	3781 (41)	3548 (42.4)	5065 (44.9)	5007 (41.7)	4350 (42.6)
Category I bites (%)	106 (1.2)	307 (3.7)	26 (0.2)	32 (0.3)	122 (1.2)
Category II bites (%)	7322 (79.4)	6257 (74.8)	9189 (81.5)	9700 (80.7)	8382 (82)
Category III bites (%)	1789 (19.4)	1806 (21.6)	2054 (18.2)	2283 (19)	2048 (20)
ERIG administered (% of Category III bites)	1445 (80.8)	1459 (80.8)	1603 (78)	1901 (83.3)	1654 (80.8)
Biting animal dog (%)	6311 (68.5)	5947 (71.1)	7768 (68.9)	7936 (66.1)	6991 (68.4)
Biting animal cat (%)	2744 (29.8)	2352 (28.1)	3429 (30.4)	3920 (32.6)	3111 (30.4)
Biting animal other (%)	162 (1.8)	71 (0.8)	72 (0.6)	159 (1.3)	116 (1.1)

TABLE 4.3 - CHARACTERISTICS OF BITE PATIENTS AND HUMAN DEATHS FROM 2019-2022.

Of the biting animals reported, most were dogs (68.4%), followed by cats (30.7%), and other species (<1%). Of the bite victims that presented to health facilities, an average of 94.3% received a full course of PEP (considered as more than 3 doses). Additionally, 80.8% of Category III bites (around 16.2% of total bite patients) received equine rabies immunoglobulin (ERIG).

4.4.2 Risk of Rabies Exposure and Human Deaths

Risk assessment data was collected for 36.3% of PHO recorded bite patients through IBCM, corresponding to 11,501 records: 3,623 (2020), 3,924 (2021), and 3,954 (2022). Of the IBCM patient records 2.2% (253/11,501) were assessed to be high-risk (5.1% were either assessed as high- or unknown-risk, 584/11,501) for rabies exposure (**Figure 4.3A**, i.e. the biting animals were considered 'probable' or 'confirmed' rabies by WHO case definitions). Of the 253 high-risk bites 199 (78.7%) were from dogs and 54 (21.3%) from cats. Most were WHO Category II (59.7%) and Category III (39.5%). At the time of the risk assessment 227 (89.7%) of biting animals had died or been killed/euthanized, and 68 (26.8%) were assessed as suspicious for rabies by the nurse or bite patient based on the animal's history, while an additional 26 (10.3%) were assessed as "sick, not rabies."

One ABTC, a major hospital located in the capital, Calapan, reported nearly complete data during the study, with 1.2% of bites assessed to be high-risk (4.2% high-risk + unknown-risk). These data represented 51.7% (5,951/11,501) of IBCM records. Extrapolating from these data to the province, an average of 284 (min=128, max=441) rabies exposures per year and 853 (min=384, max=1322) of 31,654 over the three years were estimated. When assuming only dog bites (3,945/5,951 or 66.3%) are high-risk based on RADDL records showing no cats tested positive over the last 5 years, a lower average of 1.0% (40/3,945) of bites were reported as high-risk (2.7% high + unknown-risk, 107/3,945), resulting in 134 (min=73, max=196) dog-mediated exposures per year and 403 (min=220, max=587) of 21,651 over 3-years.

During the 3 years (2020-2022), 25 human deaths were formally investigated and recorded as probable rabies cases in Oriental Mindoro and 28 animal cases were confirmed. Deaths ranged in age from 4 to 69 years (median=37 years) with 6 (25%) being <15 years and a male:female ratio of 1.08:1. Human deaths were concentrated in 8 of 15 municipalities (**Figure 4.3, B-D**), with 64% occurring in just 3 municipalities (Bongabong-6, Mansalay-5 and Pinamalayan-5). The most densely populated area, the capital city of Calapan, had zero deaths and 2 animal cases confirmed over the study period.

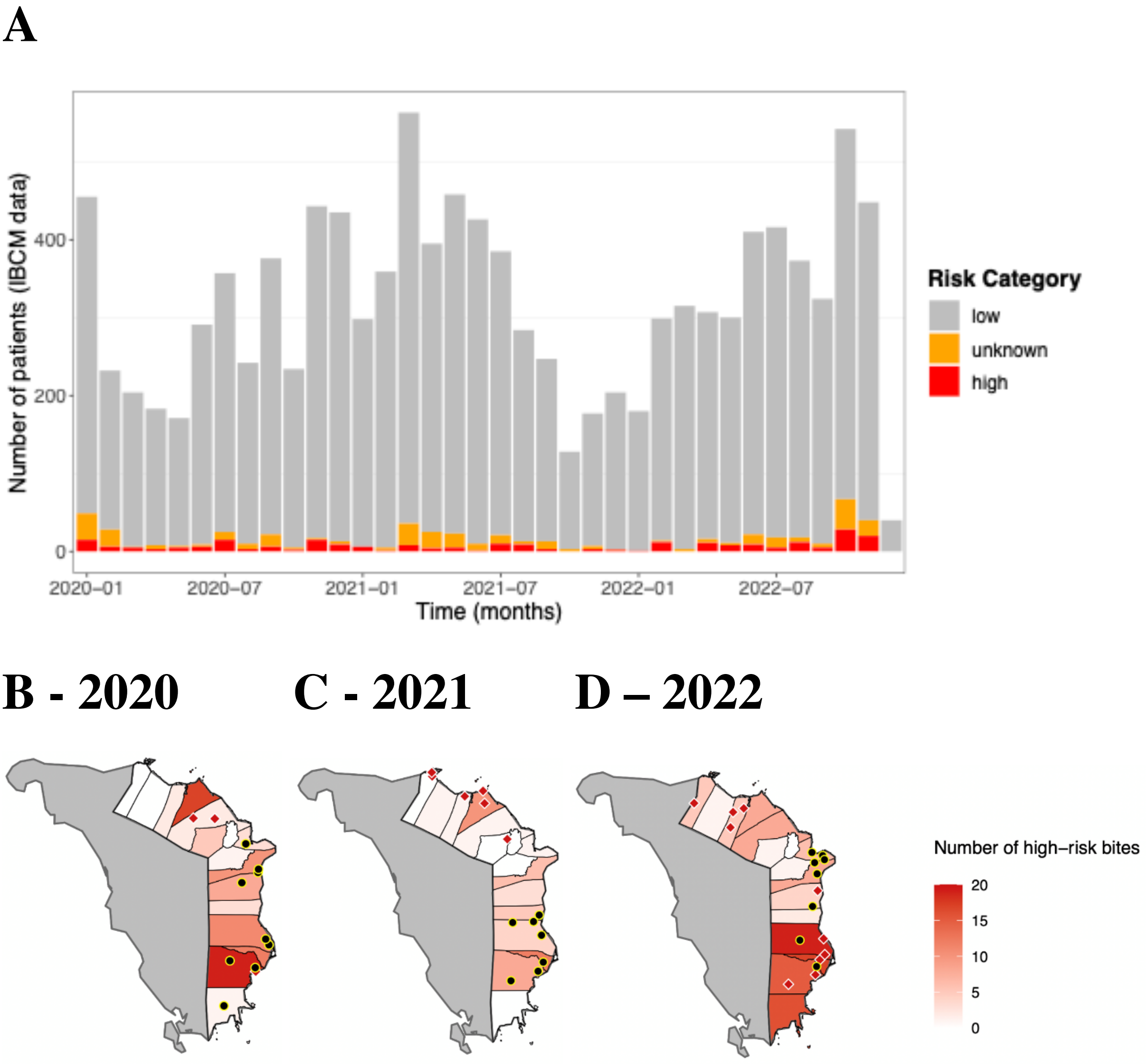


FIGURE 4.3 - SUMMARY STATISTICS OF IBCM DATA FROM ORIENTAL MINDORO PROVINCE. (A) Time series from January 2020 to December 2022, showing IBCM bite patient data by risk categories: low-risk (grey), unknown-risk (orange), and high-risk (red). (B-D) Maps showing

high-risk IBCM bite patient data by municipality and locations of human deaths and confirmed animal cases by year (B) 2020 (C) 2021 and (D) 2022.

The biting animal in all cases was a dog (72% owned, 28% unowned/stray). Of the confirmed animal cases, 57% (16/28) were found in 3 municipalities (Baco-8, Mansalay-4 and Puerto Galera-4). None of the human cases received PEP prior to displaying signs and symptoms of rabies infection. Reasons for not seeking PEP after the exposure event, as per PHO death investigation reports, included: lack of awareness of the risk of rabies from animal bites; had sought treatment from traditional healers (known as tandok/tawak in the Philippines) or were unable to find or afford PEP.

4.4.3 Decision Tree Estimations

Using the decision tree framework (**Figure 4.2**) it was estimated that an average of 211 people (95% CI 109-308) are exposed to rabies annually in Oriental Mindoro (**Table 4.4**), with an average of 69 (95% CI 42-109) of those not reporting to health facilities for PEP i.e. people exposed to rabies sought PEP with probability 0.714 (95% CI 0.599-0.779), if 90% of rabies deaths are recorded. Under this same assumption, an estimated 33 (95% CI 25-51) human deaths would have occurred over the 3 years. While the PHO records (**Table 4.3**) indicate a high incidence of bite patients exceeding 1,000 per 100,000 per year, annual rabies exposure incidence was estimated to be closer to 23 (95% CI 12-34) and 1-3 deaths per 100,000 people per year (**Table 4.4**).

The average number of rabid dogs per year in Oriental Mindoro was estimated to be 555 (95% CI 275-838), out of an estimated dog population of 141,840 (95% CI 92,540-288,500), equating to 3-5 per 1,000 dogs/year. These estimates suggest that surveillance only detected 1.65% of animal cases during the study. Though low, animal surveillance performance in terms of confirmed cases through laboratory testing increased over fivefold from 2020 to 2022 (from 0.51% to 2.85%) through implementing IBCM. However, this increase in case detection may indicate a higher incidence of animal cases in 2022 compared to 2020, rather than improved surveillance performance.

Year	**2020**	**2021**	**2022**
Recorded human deaths	**9**	**7**	**9**
Estimated human deaths	**12** [9 - 18]	**9** [7 - 15]	**12** [9 - 18]
Estimated total exposures	**225** [163 - 282]	**167** [109 - 230]	**241** [182 - 308]
Estimated exposures not seeking PEP	**73** [55 - 109]	**61** [42 - 91]	**73** [55 - 109]
Estimated exposure incidence per 100,000 persons	**25** [18 - 31]	**18** [12 - 25]	**27** [20 - 34]
Recorded rabies positive animal samples	**3**	**7**	**18**
Estimated rabid dogs	**592** [420 - 767]	**440** [275 - 642]	**632** [463 - 838]
Estimated percent animal cases confirmed	**0.51%** [0.39 - 0.71]	**1.59%** [1.09 - 2.55]	**2.85%** [2.15 – 3.89]
Estimated rabid dogs per 1000 dogs	**4.1** [1.92 - 7.45]	**3.01** [1.27 - 6.12]	**4.57** [2.06 - 7.72]

TABLE 4.4 - DECISION TREE MODEL ESTIMATES AND RECORDED DATA FOR ANNUAL BURDEN OF RABIES IN ORIENTAL MINDORO PROVINCE. Median values are in bold with 95% prediction intervals shown in brackets. Recorded human deaths are from the PHO and animal case data from RADDL.

Decision tree estimates by municipality show considerable variation in rabies burden and surveillance performance (**Table 4.5**). Estimates suggest between 3 to 60 people per 100,000 are exposed to rabies each year. Animal surveillance was weak in most municipalities, with recorded human deaths (25 total) being almost equal to confirmed animal cases (28 total) over the 3-year study. Twelve of fifteen municipalities detected <2% of estimated animal cases, of which five did not submit any samples for diagnostic testing. Two municipalities with the highest animal case detection, Baco (16%) and Puerto Galera (22.22%), did not record any human deaths.

Municipality	Human population (2020 census)	Estimated dog population	Estimated rabid dogs	Recorded rabies positive animals	Percent Rabid confirm	Estimated total exposures	Record human deaths	Estimated human deaths	Exposure incidence 100k/year
Baco	39817	5900 [4040 - 12590]	50 [19 - 92]	8	16%	19 [9 - 30]	0	0 [0 - 0]	16
Bansud	42671	6340 [4320 - 13310]	79 [48 - 136]	0	0%	29 [22 - 46]	2	2 [2 - 5]	23
Bongabong	76973	11490 [7860 - 24400]	227 [170 - 321]	2	0.88%	85 [70 - 115]	6	8 [6 - 13]	36
Bulalacao	44366	6850 [4530 - 14020]	71 [46 - 116]	0	0%	26 [23 - 42]	1	1 [1 - 4]	20
Calapan	145786	22470 [14820 - 46420]	224 [94 - 370]	2	0.89%	86 [39 - 132]	0	0 [0 - 0]	19
Gloria	50496	7880 [5150 - 15950]	92 [61 - 151]	1	1.09%	345 [28 - 52]	2	2 [2 - 5]	23
Mansalay	59114	9050 [6050 - 18340]	288 [195 - 405]	4	1.39%	109 [78 - 142]	5	7 [5 - 11]	60
Naujan	109587	16930 [11140 - 34270]	72 [23 - 135]	2	2.78%	27 [10 - 44]	0	0 [0 - 0]	8
Pinamalayan	90383	13690 [9240 - 28290]	204 [139 - 300]	1	0.49%	77 [57 - 106]	5	7 [5 - 11]	27
Pola	35455	5440 [3600 - 11250]	99 [59 - 163]	0	0%	36 [27 - 58]	3	4 [3 - 7]	33
Puerto Galera	41961	6580 [4290 - 13290]	18 [3 - 43]	4	22.22%	6 [1 - 12]	0	0 [0 - 0]	5
Roxas	58849	9120 [6000 - 18610]	162 [112 - 222]	3	1.85%	61 [48 - 76]	1	1 [1 - 3]	34
San Teodoro	19121	2990 [1950 - 6010]	27 [6 - 61]	0	0%	10 [2 - 18]	0	0 [0 - 0]	17
Socorro	41585	6260 [4230 - 13160]	11 [2 - 26]	0	0%	4 [2 - 6]	0	0 [0 - 0]	3
Victoria	52175	7980 [5320 - 16280]	23 [10 - 45]	1	4.35%	9 [6 - 11]	0	0 [0 - 0]	5
Oriental Mindoro	908339	141840 [92540 - 288500]	1678 [1218 - 2146]	28	1.67%	636 [472 - 800]	25	35 [29 - 43]	23

Table 4.5 - Decision tree estimates for the burden of rabies from Jan 2020 - Dec 2022 by municipality. Median values are in bold and 95% prediction intervals are shown in brackets. Human data is from the Provincial Health Office and animal data is from the Regional Animal Disease Diagnostic Laboratory.

From the sensitivity analysis (**Figure 4.4**), the parameters that had the greatest impact on estimates of human rabies exposures and $P_{seekPEP}$ were number of high-risk bites, followed by the probability of observing human deaths ($P_{obs|death}$).

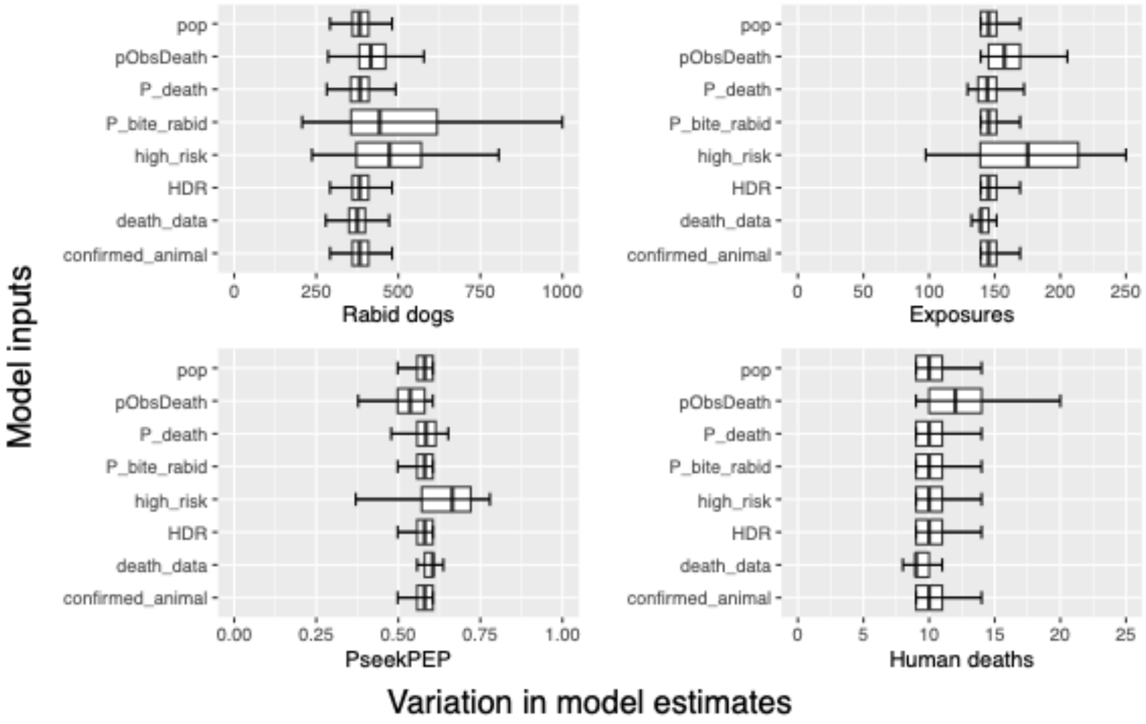


Figure 4.4 - Model sensitivity to parameter uncertainty. Panels show variation in model estimates (x-axis) under a range of parameter uncertainty (see **Table 4.2**) for each of the 8 model inputs (y-axis).

4.4.4 Economic Analysis of PEP Policies and Costs

Assuming each patient receives an average of six 0.1 ml ID injections of the vaccine (attending 3 of 4 ABTC visits) and that 80.8% of Category III bites receive an average of 2 vials of ERIG, an average PEP cost of $50.74 USD per person was calculated ($37.50 USD for those receiving vaccine only, and $127.50 USD for those also receiving ERIG). This equates to total costs (PEP and ERIG) of between $445,185 and $621,650 USD per year and >1.6 million USD over 3 years from 2020 to 2022 in Oriental Mindoro province.

This model estimated that between 18 and 28 deaths (95% CI 8-36) per year are prevented by PEP in Oriental Mindoro at an average cost of $23,110 USD (95% CI $16,730-38,240) per death averted. If IBCM was functioning effectively i.e. PEP was only provided to genuine rabies exposures, the estimated costs would be reduced to ~$3,240 USD per death averted.

With each death averted equating to approximately 37 DALYs, it was estimated that 850 DALYs are averted per year at a cost of $634 USD per DALY averted. Out of total costs, an average of 98.2% of costs for human rabies vaccine over 3 years (~$388,375 USD per year) and 87.5% of ERIG costs over 3 years (~$122,190 USD per year) was spent for bites from healthy animals that likely posed no risk of rabies.

When extrapolating across the whole country using NRPCP bite records (>1.1 million animal bites presenting to ABTCs annually), it was estimated >$55.8 million USD is spent on human rabies vaccine (>$41.2 million) and ERIG (>$14.6 million) per year. Assuming between 1-2% of bites presenting to ABTCs are probable-rabies exposures and using DOH national human death records (200-300 deaths/year), it was estimated that roughly between 1,815 and 3,630 deaths are averted by PEP each year in the Philippines at an average cost of $23,060 and $554 USD per death/DALY averted per year.

4.5 Discussion

4.5.1 Key Findings

The study results demonstrate that while overall bite patient incidence exceeds 1,000/100,000 persons per year, the majority of patients (>97%) receiving PEP in Oriental Mindoro are for bites from healthy animals. National policy mandating free provisioning of PEP and wide establishment of ABTCs have improved PEP access, averting an average of 23 deaths per year in Oriental Mindoro. However, only around 71.4% of true rabies exposures are estimated to seek PEP in Oriental Mindoro, despite this increased accessibility and availability, thus dog-mediated rabies still precipitates between 8-20 human rabies deaths each year. The human rabies burden is not distributed evenly throughout the province, with three municipalities experiencing the most human deaths over 3 years (16/25). This is likely a consequence of a combination of localized outbreaks, low dog vaccination coverage, low PEP-seeking behaviors and/or variation in surveillance and case detection capacity.

The study estimates suggest that while surveillance for human cases is relatively strong, detection of animal cases is weak, being much lower than recommendations that rabies control programs detect at least 5%, or ideally 10% of all animal cases for elimination (Townsend *et al.*, 2012). Over the 3-year study period, it was estimated there to be a total of 1,664 rabid dogs (95% CI 1,158-2,247) in Oriental Mindoro. Yet only 28 animal cases (1.68% of estimated rabid dogs) were confirmed during this time. Three municipalities confirmed more than half of the animal cases (16/28), indicating stronger surveillance, though not necessarily a higher incidence of dog rabies. IBCM surveillance protocols, encouraging the investigation of suspect rabid animals and sample collection (if dead/euthanized), facilitated a fivefold increase in the detection of laboratory-confirmed dog rabies cases from 2020 to 2022. However, with external factors such as the COVID-19 pandemic and minimal, if no, dog vaccination in 2020/2021, it is difficult to discern whether increased case detection was exclusively the outcome of enhanced surveillance or caused by increased rabies incidence in the dog population.

4.5.2 Strengths and Limitations

It was typically possible to classify biting animals as broadly “high-risk” or “low-risk” using initial patient risk assessments from IBCM, but adequate information to differentiate between WHO classifications, ‘suspect’ or ‘probable’ was not always available. IBCM protocols specified risk assessments for every bite patient presenting to ABTCs and investigations of any animal deemed high-risk. However, the COVID-19 pandemic and ensuing lockdowns contributed to challenges in the delivery of IBCM training and subsequent implementation of protocols. Heavy workloads and temporary closure/reduced operating hours of ABTCs limited the capacity of health workers to complete/submit risk assessments while movement restrictions prevented in-person animal investigations and affected sample collection.

Challenges associated with COVID-19 primarily affected IBCM implementation in 2020 and 2021, with 2022 returning to a more normal situation.

Further limitations include simplifying assumptions and uncertainties in parameters used for decision tree modeling. There was a bias towards the submission of high-risk bite data since ABTC staff were asked to prioritize, potentially leading to overestimates of rabies and exposure incidence. However, attempts were made to adjust for this by comparing IBCM data from ABTCs with limited data submission to ABTCs with near complete risk assessments for every bite patient presenting to the clinics. The probabilities that a rabid dog will bite ($P_{bites|rabid\_dog}$) and of infection following exposure ($P_{rabies|exposure}$) were from a different context (Tanzania), potentially limiting accuracy of results specific to the Philippines. While the probability of infection following exposure ($P_{rabies|exposure}$) likely has minimal variation between contexts, the probability that a rabid dog will bite ($P_{bites|rabid\_dog}$) is likely context specific due to differences in factors like the dynamics of animal/human behaviors within the community and cultural norms. Further research estimating these parameters specific to the Philippines would be useful for future studies.

$P_{rabies|exposure}$ uncertainty had little impact on model estimates, however, $P_{bites|rabid\_dog}$ affected estimates of rabid dogs and lower assumptions of $P_{obs|death}$ led to estimates of $P_{seekPEP}$ deemed implausibly low. However, it is reasonable to assume that in the Philippines a high majority of deaths are reported and captured in provincial and national statistics compared to other contexts. This means that $P_{obs|death}$ parameters used in this model are specific to the Philippines and would require adjustment when applied to settings in other countries or regions.

4.5.3 Wider Context

Results were comparable to findings from other IBCM case studies in the Philippines. A high incidence of bite patients presenting to ABTCs was found in the provinces of Bohol in 2013 (>300/100,000 persons/year) and Albay in 2018-2019 (>600/100,000 persons/year); with most bitten by healthy animals (>92% in Bohol and >97% in Albay) (Rysava *et al.*, 2019; Rysava *et al.*, 2022). Similar to the study estimates from

Oriental Mindoro province (<25 per 100,000 persons/year), these data roughly translate into an estimated incidence of rabies exposure of 24 (Bohol) and 18 (Albay) per 100,000 persons/year. This further demonstrates that while PEP-seeking behaviors have increased unsustainably in the Philippines since the initiation of the free PEP policy in 2007, the average risk of rabies exposure has remained relatively consistent throughout the country.

Moreover, while PEP administration has notably increased since the start of the NRPCP, records from the Bureau of Animal Industry indicate that animal sample submission has been declining over the last decade (NRPCP Strategic Plan, 2020). The NRPCP Strategic Plan speculates that the main reasons for this reduction are challenges with sample collection, transport, storage, and costs. Over the last decade, the number of confirmed animal cases in the Philippines has ranged from 475 to 1,227 per year (NRPCP Manual of Procedures, 2019), which is low considering that the number of animal rabies cases far exceeds the number of human deaths.

4.5.4 Conclusions & Recommendations

The NRPCP has been implementing a comprehensive package of control measures with intersectoral involvement from the national to local level and vastly improving access to PEP. However, the current surveillance system is weak, particularly for the animal sector, with the reported number of animal cases approximately equal to the reported human deaths in Oriental Mindoro. While government-allocated budgets for rabies control continually shift with different administrations, the health sector is typically funded upwards of tenfold higher than the animal health sector. For an effective rabies elimination strategy, it is imperative that dog vaccination is funded/implemented to reduce the incidence of rabies in the reservoir population. Free PEP policies, while important, will not eliminate rabies or indeed reduce the risk of exposure.

These results highlight that while current PEP policies/practices are acceptable in terms of preventing rabies deaths by improving PEP accessibility and availability, they are inefficient. Even with free provisioning of PEP, the most vulnerable populations are not seeking care (>28% of rabies exposures), suggesting alternative strategies are necessary. In accord with the WHO Rabies Modelling Consortium (2019) conclusions, this study demonstrates that for improved access to PEP to remain cost-effective, it should be implemented in conjunction with strengthened rabies surveillance that provides more accurate data on the risk of exposure for bite patients. PEP decisions should be based on risk assessments in order to reduce unnecessary spending on PEP for events that pose no risk of rabies exposure. While this study estimated a cost of $23,110 and $634 per death/DALY averted in Oriental Mindoro, the WHO Rabies Modelling Consortium study suggests that using efficient ID regimens (already used in the Philippines) along with risk-based assessments may result in costs as low as $635 USD and $33 USD per death/DALY averted.

In conclusion, the findings from this chapter demonstrate the wider benefits of integrating a One Health IBCM approach into national policy in the Philippines. If implemented effectively, IBCM has the potential to guide judicious PEP administration, thereby improving cost-effectiveness and allowing the reallocation of funds to the animal health sector for dog vaccination – the most effective way to eliminate rabies. Moreover, IBCM can provide more accurate data on the circulation of rabies to inform control of rabies through mass dog vaccination and help achieve/maintain rabies elimination in the Philippines.

CHAPTER 5

A discussion of implementing intersectoral surveillance for rabies control and elimination

This thesis demonstrates that while the establishment of an IBCM surveillance system is both beneficial and necessary for countries seeking to achieve *Zero by 30* goals and receive WHO validation of freedom from human rabies deaths, implementing IBCM effectively is challenging. Around the world, endemic LMICs face various barriers preventing the successful delivery and integration of a One Health IBCM approach into their national rabies control strategies. For IBCM implementation, the Philippines has the necessary infrastructure (i.e. ABTCs and diagnostic laboratories); workforce capacity (i.e. trained health workers); and government engagement and support at the national level (i.e. well-established national strategy in place). Despite this, delivery of IBCM using existing government staff in Oriental Mindoro province was not feasible and protocols were not adopted as a level sufficient for sustainability without continued external support and funding from the research project. IBCM data collected in Oriental Mindoro province over the three-year study period showed that >97% of bite patients receiving rabies were for bites from healthy animals with no risk of rabies. This indiscriminate provisioning of PEP resulted in substantial expenditure on PEP (>$535,000 USD per year), using limited funding that could have been invested in vaccinating dogs to reduce the incidence of rabies in the reservoir population, and thus the number of human exposures.

A study conducted by the WHO Rabies Modelling Consortium (2019) showed that expanding access and free provisioning of PEP using ID regimens can be an extremely cost-effective ($635 and $33 USD per death/DALY averted) strategy, reducing the burden of rabies while leaving funding available to scale up mass dog vaccination. Yet, the Philippines—where ID regimens are already used nationwide—is one example where extremely high bite patient presentations (1,160/100,000 persons/year) and awareness of rabies have led to excessive and unsustainable spending on PEP i.e.

$23,110 and $634 USD per death/DALY averted, despite using more efficient ID regimens. Even if the Philippines switched from the 4-dose Thai Red Cross intradermal (ID) regimen (days 0, 3, 7 and 28) to the 3-dose 1-week ID regimen (days 0, 3, 7), the cost savings would be minimal. However, if the Philippines used risk-based protocols to make PEP decisions (i.e. only providing PEP to bite patients with genuine risk of rabies exposures), the cost per death averted could be reduced to ~$3,240 USD. In Chapter 4, it was estimated the Philippines spends >55 million USD each year on PEP, averting an average of 2,720 death annually. If the NRPCP integrated protocols using patient risk assessment to make PEP decisions more judiciously, this same number of deaths could be averted whilst reducing PEP expenditure by at least half.

The extent of success towards rabies elimination can be largely boiled down to decisions a country makes about where to prioritize investment. Broadly speaking, many Asian countries have invested strongly in improving the accessibility and availability of PEP to reduce human deaths but have provided little funding for MDV or the animal health sector. While access to PEP is imperative, this tactic cannot be solely relied upon to eliminate human rabies deaths. Even with free PEP and extensive awareness, PEP-seeking behaviors for rabies exposures will never reach 100%, particularly for vulnerable populations experiencing inequalities in healthcare (Etheart *et al.*, 2017; Changalucha *et al.*, 2018). This point is demonstrated in Chapter 4, where despite a high incidence of patients presenting to ABTCs in Oriental Mindoro, there was still a high burden of human cases (1-3 deaths per 100,000 people/year) due to >28% of estimated exposures not seeking PEP. Additionally, provisioning of free PEP without risk-based assessments and close integration of involvement from the veterinary sector can easily ingrain high PEP-seeking behaviors for bites with no meaningful risk of rabies, leading to unsustainable expenditure while unnecessarily draining finite health budgets (Rysava *et al.*, 2019; Lechenne *et al.*, 2017; Rajeev *et al.*, 2019).

Dog rabies has been researched in the laboratory and field and successfully eliminated for over a century, even in the absence of modern technologies (e.g. mobile applications tracking data, LFDs, microchipping of dogs, etc.). Given that rabies is vaccine-preventable and has a low R_0 with highly localized transmission dynamics, in theory, it should be straightforward to control with minimal effort. Moreover, the fact that >99% of human deaths (WHO TRS, 2018) result from bites from domestic dogs makes tackling rabies as a public health threat feasible through two concurrent interventions: 1) annual vaccination of dogs sustaining 70% vaccination coverage, and 2) providing prompt administration of PEP to exposures to avoid human deaths while rabies incidence is being reduced (Cleaveland *et al.*, 2006; WHO Rabies vaccines, 2018; Lavan *et al.*, 2017). The obvious solution is to provide enough funding and support for comprehensive annual MDV campaigns, conducted homogeneously throughout the world, limiting re-emergence and incursion events from bordering areas. After all, as one of the few zoonoses with official elimination goals set by WHO, rabies control programs should urge prioritization of investment. However, like all disease elimination strategies, particularly for NTDS, distributing funding for evidence-based interventions requires more than resources to be effective.

The *Zero by 30* strategy advocates IBCM as a potentially cost-effective solution to enhance surveillance to monitor, evaluate, and guide rabies control and elimination efforts. However, like other rabies control measures i.e. MDV and PEP provisioning, IBCM faces implementation challenges of its own in LMICs. In Chapter 2, the comparison of fourteen IBCM programs across Asia, Africa, and the Americas illustrated variations in barriers and facilitators to implementing IBCM effectively in different geographical locations. The findings from this Chapter showed that settings with comparable contextual features experienced exceedingly similar barriers limiting the feasibility of IBCM delivery. This study only skimmed the surface in terms of how the operationalization of IBCM programs fluctuates between different regions, countries, and subregions. This may have been the first paper to demonstrate the importance of implementation research in transferring the evidence base of the IBCM approach to inform adaptations when implemented in a new context to ensure effectiveness (Copeland *et al.*, 2021; Swedberg *et al.*, 2022). While the results have identified the necessity of adapting protocols to fit the local context to facilitate the uptake, integration, and sustainability of IBCM practices, there remains little guidance on this. These findings point to the recommendation that international organizations should provide tools to guide the tailoring of the development and implementation of IBCM programs to adjust protocols to fit a variety of settings. This could be of vital importance for current and newly established national rabies programs adopting the IBCM approach as part of their strategy to reach 2030 elimination targets.

The Philippines, in many ways, is an ideal location to conduct an implementation study of IBCM, evaluating how to adapt protocols to effectively integrate IBCM practices. The long-established national rabies program (NRPCP) is internationally acclaimed (WOAH, 2021), and has delivered a comprehensive package of control measures since 2007. Though, despite decades of building a network of >500 ABTCs with free provisioning of PEP, dedicating the month of March to rabies awareness/educational and MDV campaigns, and training health workers, the country still suffers from endemic dog-mediated rabies (Amparo *et al.*, 2018; NRPCP Strategic Plan, 2020). This existing infrastructure, workforce, and commitment provide a solid foundation for the integration of IBCM, which appears like it could be a missing link that could propel the Philippines towards rabies elimination. Enhancing the sensitivity and robustness of surveillance through IBCM addresses the primary issues faced in this archipelagic nation by 1) using risk-based assessments to make PEP decisions to improve patient care and reduce expenditure on unnecessary PEP, and 2) rapidly identifying suspected rabid animals to increase animal case detection for targeting high-risk areas. Yet, while IBCM sounds ideal, the question is how can existing government staff be convinced to uptake protocols and a well-established national program to integrate new practices into their policy.

The mixed methods evaluation of IBCM implementation in the province of Oriental Mindoro from Chapter 3 showed that while these are perhaps simple questions, the answers are quite complex. IBCM was found to be highly acceptable by trained government human and animal health workers, but despite this perceived value and enthusiasm for IBCM, practices were not appropriate for the setting due to barriers preventing the adoption of protocols. Initial assumptions that health workers would perform risk assessments for all bite patients and the animal health sector would be informed of, conduct, and submit investigation data for all suspected rabid animals were unrealistic. The added complication of the COVID-19 pandemic at the start of the project did not help matters. Yet, even prior to the pandemic, there was evidence that the initial project design envisioned was not feasible. While key adaptations made to IBCM protocols over the course of the study (i.e. project staff being proactive to conduct most IBCM activities and liaison reports/updates between sectors) led to successful outcomes, the study was limited in terms of developing best practices for national integration. Despite this, IBCM showed great promise as an intervention in the Philippines if delivered effectively. Expansion of IBCM implementation to three additional provinces in the MIMAROPA region (2023-2026) aims to generate further evidence of this and build upon lessons learned for adaptation and scale-up.

Yet, the political climate and changes in government administration in the Philippines beginning in 2023 may have major implications for the direction of the NRPCP and willingness to integrate IBCM. Recently, the NRPCP has been in the spotlight of national news, with a few members of the newly appointed government stating it is a failed program. In a November 2022 article, a District Representative stated *"The NRPCP has missed its targets to eliminate human rabies by 2020 and to declare the Philippines rabies-free by 2022, despite ample funding of between P500 to P900 million every year. We want the NRPCP's failure investigated, with a view to recommending stronger corrective measures to finally eliminate human deaths from rabies in the country"* (Quismorio, 2022). As of now, it is difficult to say whether an investigation of the NRPCP would lead to a positive upshift in NRPCP policies, with a willingness to integrate new approaches like IBCM, or to a detrimental defunding of the program. Either way, it is fair to say that integrating IBCM into national policy in the Philippines could be an arduous undertaking, particularly with the politically decentralized governance that formally delegates the power to act on rabies control measures to the local government units (NRPCP MOP, 2019). The complicated administrative divisions comprising 18 regions, 81 provinces, 1,488 municipalities, and 42,029 barangays, make it vitally important that IBCM is advocated nationwide through the NRPCP supported by the DOH and DA (PhilAtlas, 2023).

At the end of 2022, the IBCM implementation project in the Philippines encountered these glaringly apparent challenges firsthand due to the decentralized governance model. While this thesis only discusses the province of Oriental Mindoro, the IBCM study was also conducted in a second adjacent location in the MIMAROPA region, the island province of Romblon, which was declared rabies-free by the NRPCP in 2018. Around October 2022, the IBCM surveillance and project team detected numerous high-risk bites leading to the first confirmed animal rabies case in the province in more than seven years. As of March 2023, there have been >30 laboratory-confirmed rabid dogs detected within the timespan of about five months. Upon attempting to receive national government support to contain this outbreak, it was discovered that policy mandates the declaration of an outbreak by a municipal government is only possible for infectious diseases with human-to-human transmission. Additionally, the decision to fund emergency mass dog vaccination must be made on a per municipality-level basis (Romblon has 17 municipalities), which drastically reduces the potential for island-wide coordination of efforts through the provincial government. The silver lining is that IBCM surveillance was able to detect this incursion relatively quickly and draw attention to the situation using quantitative evidence generated from in-field testing with RDTs and laboratory testing for confirmation.

One of the best ways to persuade the national government to adopt IBCM is by convincing them through tangible quantitative evidence revealing the value of this approach, such as results from Chapter 4. This Chapter demonstrated how IBCM risk assessment data could be used to estimate the burden of rabies, current surveillance performance, and costs/benefits of current PEP policies. Decision tree estimates from Chapter 4 were made using relatively straightforward calculations, aiming to provide local practitioners and stakeholders with a better perception of the burden of rabies in their area. This was valuable both in terms of adjusting their expectations of how much work was required from them (i.e. how many bites are likely to be genuine exposures/how many animals are likely to be rabid per month and year) and providing feedback on their efforts to promote motivation and engagement with the project and a better understanding of the impact from IBCM. Uncertainty in parameters and data quality used in the model limited accuracy of estimations. However, using the number of reported human deaths alone, the predicted minimum number of rabid dogs persisting in the population annually was surprising to most local stakeholders in Oriental Mindoro. While future research is needed to refine this model and integrate better data on the dog population (i.e. the number of susceptible dogs), these initial estimates are a valuable starting point to advocate for more funding, resources, and support for MDV campaigns.

When I started my PhD over three years ago, there were only a handful of papers available about the One Health IBCM approach that I would be studying over the entirety of my thesis. While IBCM itself has been used as a standard operating protocol for several decades in Western Europe, the United States, and Canada, its rebranded approach used to enhance surveillance in LMICs is still quite novel. *Zero by 30* has amplified attention and the call for countries to establish national programs in attempts to eliminate rabies, in which IBCM will be a key component. Without sufficient surveillance in place, WHO will not be able to verify that 2030 elimination goals have been met. Therefore, every country aiming to have zero human deaths from dog-mediated rabies will need an effective IBCM surveillance system in place as part of its national rabies control strategy. IBCM programs in different settings will have varying desired outcomes as seen in Chapter 2. Some settings may find it useful to quantify the burden of rabies using methods similar to Chapter 4, while other contexts might find IBCM to be most valuable as a tool for assessing risk to make PEP decisions, such as the Philippines. No matter the aim, the successful implementation of IBCM using evaluation methods seen in Chapter 3 is of vital importance moving forward to progress towards a world free of human deaths from dog-mediated rabies by 2030.

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Appendix 1

Country	Continent	Population (2020)	GDP (2020, US$/Bn)	HDI (2019)	Rabies elimination stage	Level of dog vaccination	Owned, free roaming dogs	Deaths per year	Policy on PEP (cost per course)	Bite incidence (per 100k)	Estimated HDR ***	Source
Chad	Africa	16,425,860	10.1	0.40	Endemic	Not routine	>90% >90%	550	Patient pays* (US$ 80-100)	480-570	1: 7.8 (1: 5.2-40)	(10) (22) (23) (24)
Kenya	Africa	53,771,300	98.8	0.60	Endemic	Not routine	>90% >90%	2,200	Patient pays* (US$ 85)	290	1: 4-8	(22) (25)
Madagascar	Africa	27,691,020	13.7	0.53	Endemic	Not routine	>90% >90%	1,000	Free	190	1: 8-25	(26) (27)
Malawi	Africa	19,129,955	12.0	0.48	Endemic	Not routine	>90% >90%	900	Free	230	1: 23 (1: 14-31.8)	(22) (28)
Tanzania	Africa	59,734,210	62.4	0.53	Endemic	Not routine	>90% >90%	650	Patient pays (>US$ 80)	12-120	1: 20.7 (1: 7-181.3)	(9) (22) (29)
Brazil	Americas	212,559,410	1,445.0	0.77	Elimination*	Routine*	>90% <50%	<10	Free	230-280	1: 4.2-7	(30) (31)
Guatemala	Americas	16,858,330	77.6	0.66	Endemic	Routine	>80% >70%	0-8	Free	150-280	1: 6.4 (1: 1-10)	(30) (33) (34)
Haiti	Americas	11,402,530	13.4	0.51	Endemic	Routine	>90% >50%	350	Free	200	1: 5.2	(22) (35)
Peru	Americas	32,971,850	202.0	0.78	Emerging*	Routine	>80% >40%	0-10	Free	200-600	1: 3.8	(30) (36) (37)
India	Asia	1,380,004,390	2,623.0	0.65	Endemic *Goa State - elimination	Highly variable	>60% >40%	>15,000 *Goa State: 0 since 2018	Free	1,300	1: 11-36	(22) (38) (39)
Indonesia	Asia	273,523,620	1,058.0	0.72	Endemic*	Not routine	>90% >70%	3,300	Free	200	1: 8.3-360	(22) (41) (42)
Philippines	Asia	109,581,090	361.5	0.72	Endemic	Routine but variable	>80% >50%	200-300	Free	1,100	1: 4-10	(43) (44) (45)
Vietnam	Asia	97,338,580	271.2	0.70	Endemic	Routine but variable	>80% >50%	500	Patient pays (US$ 150)	400	1: 10-38	(22) (46) (47) (48)

TABLE 2.1. ECONOMIC AND EPIDEMIOLOGICAL CONTEXT OF COUNTRIES INCLUDED IN THIS STUDY. GDP = Gross Domestic Product, HDI = Human Development Index, PEP = post-exposure prophylaxis, HDR = Human to Dog Ratio. Population and GDP data from the World Bank OECD National Accounts data files, 2020 (https://data.worldbank.org). HDI data from the United Nations Development Programme 2020 Human Development Index Ranking (https://hdr.undp.org). This table was made following participant interviews to show variation in socioeconomic status between IBCM program locations. Rabies elimination stage, level of rabies control, and policy on PEP were all reported from interviews. Deaths per year, annual bite patient incidence, and estimated human:dog ratios were from the literature. *Brazil is close to elimination, but rabies has continuously circulated in the state of Maranhão (32). *Peru is close to elimination, but rabies has continuously circulated in the border state of Puno and re-emerged in the city of Arequipa in 2015 (37). Canine rabies is endemic in India, but the State of Goa is now close to elimination and has not had a human rabies death since 2018 (40). Indonesia has endemic dog rabies in 26 provinces, while 8 provinces are rabies-free (41). *Dog vaccination is routine in 24/27 Brazilian states, but has been discontinued in 3 southern states: Paraná, Santa Catarina and Rio Grande do Sul. There is considerable variability in the degree of routine dog vaccination reported in Asian countries. *Patients pay for PEP in Chad, but PEP was provided for free during the IBCM project (2016-2018). *Patients pay for PEP in most of Kenya, but PEP is free in a few counties (e.g., Makueni). Bite patient incidence (presentations to health facilities) is reported rather than cross-sectional surveys which typically are much higher. *** Variability in HDRs relates to culture (with major differences between religions).

Appendix 2

Code	**Sub-code**
Expert's background	• Education • Occupation • Experience with IBCM (countries/years)
Understanding of IBCM	• Definition or Description • Differentiation • History of IBCM • Appropriateness
Implementation of IBCM	• Context • IBCM Development • Training • Adaptations • Barriers • Facilitators
Post-exposure prophylaxis (PEP)	• Accessibility & Availability • Affordability & Cost • PEP adherence • Judicious PEP • Health-seeking behaviors
Surveillance	• Human exposures or bites • Animal case detection • Human deaths • Incursions • Verify elimination • Diagnostics (RDTs, PCR, samples)

‘One Health’ collaboration	• Designated workforce • Intersectoral collaboration • Reporting probable rabid bites • Reporting suspect animals • Feedback & communication
Risk assessments	• Knowledge of animal & human rabies • Recording bite patient data
Animal investigations	• Finding animal • Quarantining animal • Collecting/ sending samples • Recording animal data
Rabies policies	• Incentives • Free PEP • Notifiable disease • Education campaigns • Responsible pet ownership • Mass Dog Vaccination (MDV) • Culling • Funding
Mobile technology	• Opportunities • Challenges
Impact of COVID pandemic	• Program implementation • Resources/priorities • Livelihood

Table 2.2. Code framework for thematic analysis used in Chapter 2

Appendix 3

Country	Continent	Population (2020)	GDP (2020, US$/Bn)	HDI (2019)	Rabies elimination stage	Level of dog vaccination	Owned, free roaming dogs	Deaths per year	Policy on PEP (cost per course)	Bite incidence (per 100k)	Estimated HDR ***	Source
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TABLE 2.3. COMPARISON OF OPERATIONALIZED IBCM PROGRAMS. Information collected through interview data. *IBCM programs in Guatemala and Peru have started training and pilot studies, but implementation was delayed due to COVID-19. IBCM is not being used yet and both countries are still relying on passive surveillance to find rabies cases. *Chad's IBCM program was implemented in 4 administrative regions: Logone Occidentale, Ouaddaï, Hadjer Lamis, and Chari Baguirmi (21). Tanzania's IBCM program is implemented in 4 regions: Mtwara, Mara, Lindi, and Morogoro (13). Brazil does not have an official IBCM program, but similar protocols are implemented in 3 states in the South Region: Paraná, Santa Catarina and Rio Grande do Sul (interview data). Vietnam's IBCM program is currently implemented in 5 provinces in Central and Northern Vietnam: Phú Thọ, Bà Rịa-Vũng Tàu, Nghệ An, Lạng Sơn and Đắk Lắk and will be expanded to a further 4 provinces in 2022, which includes Southern Vietnam (interview data).

Appendix 4

	Risk Assessment	PEP Provisioning	Animal Investigation	One Health collaboration	Data reporting/mobile technology
Barriers	**Govt health workers:** Work Capacity • Busy workload • High patient volume • Many responsibilities • Other priorities • Work duplication Human & Financial Resources • High staff turnover • Not compensated for additional IBCM work Compliance with guidelines • Felt rabies not their job • Reluctance to change or adopt new routine Performing risk assessment • Limited knowledge of rabies incl. WHO Categories & signs of rabies in animal • Focus on wound severity not rabies signs in biting animal Judicious use of PEP • Hesitancy to discontinue or withhold PEP • No legal basis for risk assessment to inform PEP	**PEP accessibility:** Costs • High out-of-pocket costs of PEP • High travel costs to closest clinic w/ PEP Access • Most vulnerable populations don't have access to health services **PEP availability:** • Frequent stockouts • Not available in many rural/remote areas **Excessive PEP use:** • Free PEP policy can lead to excessive PEP-seeking behavior • Indiscriminate PEP use can cause excessive costs/ stockouts • Same or more demand for PEP even when low or zero risk of rabies **Local beliefs:** • Seeking care at traditional healers	**Govt animal health workers:** Compliance with guidelines • Investigations late or not conducted • No follow-up • Reluctance to change or adopt new routine • Felt rabies not their job • Other prioritizes • Not motivated to investigate until death Human & Financial Resources • Lack of personnel • High staff turnover • Not compensated for time or travel costs Training • Lack of formal training • Not comfortable handling animals **Conducting animal investigation:** • Cannot find or identify biting animal • Not able to get sample **Diagnostics:** • Few diagnostic lab(s) • Must ship samples far without cold chain	**National-level:** Governance structures • Govt ministry not structured for One Health • Lack of ministry cooperation • Unbalanced sector power Policy • Rabies neglected/not priority • Lack of funding • Difficult integrating IBCM into national policy **Regional / Local-level:** Compliance with guidelines • Health sector not notifying about bites • Investigation results not considered for PEP decision Stakeholder Engagement • Lack of local ownership • No prior intersectoral communication • Difficult to change routine behavior • Difficult to establish and maintain communication Required Skills • Limited experience with data management	**Data reporting:** • Lack of data submission by both sectors • Feedback not provided to other sectors • Investigation case not formally closed **Mobile technology:** App issues • App development timely and many iterations • App not feasible in all settings – e.g., high illiteracy/no written language • Limited network coverage • App must be updated and re-downloaded User Issues • Lack access to smartphones/tablets • Reluctance to use app • Required additional proficiency training
Facilitators	**Workforce:** • Hiring staff to perform risk assessments • Consistent feedback and communication **Training & Materials:** • Apps that automatically assign case definition • Provision of hard copy protocols • Routine training	**Free PEP policy:** • Increased accessibility • Increased PEP-seeking • Increased PEP adherence **Community Outreach:** • Educating local traditional healers to report bites	**Workforce:** • Hiring staff to conduct animal investigations **Training & Materials:** • Hook and straw sampling techniques • Rapid diagnostic tests • Safely handling animals **Communication:** • Prepare stakeholders for swift rise in case detection	**Communication:** • Consistent feedback with all involved sectors • Establishing hotline to facilitate One Health link **Collaboration:** • Involving all sectors in discussions/decisions • Using existing One Health programs and networks • Employing veterinary staff within public health system	**Communication:** • Consistent feedback/ reminders to report **Mobile technology:** • Real-time data monitoring • Remote data access • Quick way to establish a surveillance system • Overcome language barriers

TABLE 2.4. BARRIERS AND FACILITATORS TO IMPLEMENTATION OF IBCM PROGRAMS. Summarizes key barriers and facilitators for five categories: risk assessment, PEP provisioning, animal investigation, One Health collaboration, and data reporting/ mobile technology.

Appendix 5

Context (barriers & *facilitators*): High use of costly PEP; Low detection of animal rabies cases; Occasional human rabies deaths occur; Limited surveillance guidance to inform dog rabies control programmes; Unable to verify freedom from disease; Limited contingency planning for outbreak response**;** Weak rabies surveillance system; Poor implementation of RA 9482 (Philippine Rabies Act); Lack of budget for PEP; Not all surveillance officer are trained on IBCM at local government level; No continuous advocacy on responsible pet ownership and rabies awareness; No available diagnostic test in the island; Not implaced serviced delivery network for bite cases and immediate suspected rabies cases esp in the island municipalities; One health program is not yet integrated in the island animal health sector; Poor animal vaccination coverage; Lack of manpower from animal sector; *highly successful bottom-up approaches that entails collaboration across various sectors; national program aligned with the regional Asian roadmap towards rabies control and elimination*

	Resources and Programme inputs	**Logic of Change**			**Outcomes**		**Goal**
		Train participants and provide resources	**Implement IBCM and Rationalized PEP**	**Participants Maintain IBCM and Rationalized PEP**	**Short term**	**Longer term**	**Guide and sustain the elimination of rabies in the Philippines through the establishment of a cost-effective, epidemiologically robust, and enhanced disease surveillance and response package**
	Relational: 1) Institutional commitment (National, Provincial, Municipal) to support programme **Physical:** 1) Training & certification materials; 2) Refined protocols, (IBCM risk assessment, PEP administration, Outbreak investigations, reporting); 3) Technologies (Mobile App, Rapid Diagnostic Tests (RDTs), Portable Sequencing, Bioinformatics pipeline, Genomic Database, Data Vizualization Platform) **Financial:** Funding to pay for training, materials, time, activities, communications **Human**: 1) Programme expertise and support	Recruit frontline health and animal health workers responsible for implementing surveillance: 1) Draw on workers interests and motivations; 2) Reassure workers that intervention not dissimilar to status quo. Train and certify frontline workers to proficient standard and update devices: 1) Functional database and surveillance forms developed by computer scientist with support of epidemiologist; 2) Participants trained in revised protocols, procedures using relevant devices; 3) Provision of materials, SOPs and equipment	**Deployment of functioning real-time surveillance & response system**: 1) Frontline workers have knowledge, skills, confidence, & motivation to follow new SOPs; 2) Frontline workers follow SOPs and record data using digitial devices and configured forms; 3) Alerts are promptly transmitted through digitial devices and infrastructure; 4) Trained epidemiologist receives, analyses and interprets surveillance; 5) Epidemiologist shares results with frontline workers who adhere to SOPs; 6) Epidemiologist shares data with relevant institutions	**Routinisation into daily activities**: 1) Improved working relationship between human and animal health workers; 2) Improved data & understanding of local rabies situation	**Evidence and replication plans**: 1) Reduction in PEP use & costs; 2) Data identifies high-risk exposures; 3) Active (& increased) case investigation; 4) Guidance for replication developed; 4) Provide evidence to inform policy-making in NRPCP	**A proven template and best practice developed for improving clinical practice, demonstrating and sustaining freedom from rabies and realising cost savings for NRPCP:** 1) NRPCP scale up; 2) Provincial & Municipal offices allocate budget for surveillance operations	
Mechanisms	Inputs provided are sufficient to adequately train and support participants and all required materials provided		1) App is used for IBCM & field investigations 2) Risk assessment informs PEP administration 3) Suspicious bites trigger investigations 4) Quarantine/observation gives confidence in withholding PEP 5) Real-time sequencing informs geographic risk assessment		Maintenance of implemented IBCM and rationalized PEP is evaluated to provide adequate evidence and replication plans	Evidence and replication plans are disseminated to national, provincial and municipal levels with engagement to support roll-out	

TABLE 3.1. INITIAL PROJECT THEORY OF CHANGE (2019)

Appendix 6

Interview Question	Follow-up Questions
1. What is your understanding of IBCM?	- What do you think is the overall impact of IBCM? - Do you think it's important? - What do you think are its benefits?
2. Experiences implementing IBCM so far	- How is it different from how you used to do rabies work? - Changes in routine - Changes in relationships with colleagues
3. Speaking of colleagues, do you think your colleagues understand IBCM?	- How do they accept it? How they perceive it? - Do they know their roles? - Was there anyone serving as a champion in implementing IBCM? - Were there any systems set up for reinforcement/reminders?
4. Do you hear your colleagues giving feedback about IBCM (processes and the work they have to do)?	- Do they think it is a worthwhile endeavor? - Do you think giving feedback can be used to improve the implementation?
5. Did you find it easy to integrate/implement IBCM?	- How were the adjustments? - Was it easy to stick to the protocol or did you have to make changes?
6. Are you confident in you and your office's ability to implement IBCM?	- How about your colleagues' abilities? - Do they have the necessary skillset and training?
7. Do you think you have enough training and resources to implement IBCM?	- Enough support from the management/government? - Did you ever need external help?
8. Barriers and Facilitators in implementing IBCM (if not already addressed earlier)	- Individuals, organizations - Geographical (distance, road infrastructure, etc.) - Resources (money, time) - Political (stakeholders/laws/ordinances) - Attitude of people, local communities, human-dog relations
9. What has surprised you? Anything notable/interesting stories to share?	

TABLE 3.5. INTERVIEW TOPIC GUIDE FOR CHAPTER 3