Canine rabies control and management in Southeast Asia: from data to models.

By

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Věnováno tátovi, hloupému slůněti.

Navždy jsi v mém srdci. Chybíš mi.

Dedicated to my dad, the silly elephant.

You are forever in my heart. I miss you.

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I declare that the work presented in this thesis is the result of original research conducted and composed by the author, Kristyna Rysava, except where otherwise stated. The copyright of this thesis belongs to the author under the terms of the United Kingdom. Copyright Acts. Due acknowledgement must always be made of the use of any material contained in, or derived from, this thesis.

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I further declare that no part of this thesis has been previously submitted, at the University of Warwick or elsewhere, for examination that would lead to the award of a diploma or degree.

Abstract

Canine rabies is a significant public health concern and economic burden in most low- and middle-income countries across Africa and Asia. Global targets for elimination of dog-mediated rabies have been set for 2030. Though fatal once clinical symptoms appear, rabies is preventable through appropriate administration of human and dog vaccines. Post-exposure prophylaxis (PEP) is highly effective in averting the onset of rabies if delivered promptly after a person is bitten by a rabid animal. However, its unequal distribution creates disparity between settings. Where access to PEP is limited and the personal costs prohibitive, many people die having been refused appropriate healthcare. On the other hand, indiscriminately administered PEP results in excessive expenditure on non-case patients, subsequent financial strains and vaccine shortages, whilst vulnerable communities remain untreated. The lack of formal surveillance leads to suboptimal detection of the disease, preceding unrestricted transmission and misleading representation of its magnitude, undermining advocacy for funding of control programmes. While mass dog vaccination can eliminate rabies from the source population, it requires extensive resources and is currently not conducted systematically and at scale in most rabies endemic countries.

The main objectives of this thesis were first to critically review and evaluate accomplishments and failures of the existing rabies control and management strategies in Southeast Asia (Chapters 1 and 2), and secondly to use these assessments to draw and test potential improvements to accelerate the elimination targets across the region (Chapters 3 and 4). We used a combination of long-term epidemiological datasets, experimental design and theoretical models to examine the theory and implementation of intersectoral, enhanced surveillance and dog quarantine in the context of canine rabies in domestic dogs.

Several key themes have emerged from this work. First and foremost, to eliminate rabies will require time, resources and commitment as well as a combination of strategies following the One Health concept. An effective One Health approach entails long-term planning, intersectoral communication and collaboration, and sustained effort using tried and tested methods.

Efforts should be directed towards well-coordinated high-coverage annual dog vaccinations using high-quality vaccines and enhanced surveillance targeted through investigations of biting animals. The logistics of vaccinating a very large, free-roaming dog population that is typical of most Southeast Asian countries may be challenging but certainly not impossible. Lessons can be drawn from Bali, Indonesia for other large and dense dog populations, where dog management and rabies control appear difficult. Well-trained teams with nets can rapidly catch and vaccinate large numbers of dogs where central-point vaccinations are insufficient, and post-vaccination surveys of collared dogs can be used to evaluate coverage and target supplementary vaccinations. However, careful planning is required to ensure all communities are reached during campaigns and sufficient vaccine is available over consecutive years. Effective communication strategies are needed to coordinate intersectoral activities, and to keep communities as well as rabies practitioners engaged.

Using detailed questionnaires on animal bite histories combined with phone follow-ups and field investigations, we demonstrated the effectiveness of Integrated Bite Case Management (IBCM) in detecting rabies in the dog population, offering a more sensitive alternative to routine surveillance conducted at random. We noted that the reported patient bite incidence reflects the availability of the vaccine and proximity of bite patients to clinics rather than the actual disease incidence in the dog population and should not be taken as an indicator of rabies burden alone without further field investigations. In fact, rabies transmission between dogs appears to take place mostly locally with cases from neighbouring areas, and focal cases from the previous month having been most significantly predictive of future rabies occurrence both in Bali and the Philippines.

We advocate that joint investigations such as Integrated Bite Case Management have the potential to foster intersectoral relationships, opening much needed space for collaborative investments between public health and veterinary services. Triage of patients and investigations of suspect dogs offer an effective tool for improved PEP recommendations and reduction of potentially unnecessary expenditures and can provide real-time guidance for tailored quarantine of high-risk contacts. Temporary exclusion of infected dogs appears powerful in curtailing rabies transmission despite the low prevalence of the disease,

particularly in settings where optimal vaccination coverage is yet to be achieved, providing a critical stopgap to reduce the number of human deaths due to rabid bites.

We conclude that all of the control and prevention activities discussed in this thesis will be necessary for complete interruption of transmission of the virus and sustained elimination of rabies, especially given the enduring risk of re-introductions from neighbouring populations.

List of Abbreviations

ABC	Animal Bite Center
ABTC	Animal Bite Treatment Center
AIC	Akaike Information Criterion
AUC	Area Under Curve
BAWA	Bali Animal Welfare Association
BITERS	Bite Incidence Tool for Enhanced Rabies Surveillance
BRTTH	Bicol Regional Training and Teaching Hospital
BSREC	Biomedical and Scientific Research Ethics Committee
DIC	Disease Investigation Centre
FAO	Food and Agriculture Organization
FAT	Fluorescent Antibody Test
IBCM	Integrated Bite Case Management
ID	Intradermal(ly)
IM	Intramuscular(ly)
JBDMDH	Josefina Belmonte Duran Memorial District Hospital
LGU	Local Governmental Unit
LIMICs	Low and Middle-Income Countries
MDV	Mass Dog Vaccination
ODEs	Ordinary Differential Equations
OIE	World Organisation for Animal Health
PEP	Post-exposure Prophylaxis
PHREB	Philippine Health Research Ethics Board
PVS	Provincial Veterinary Services
RABV	Rabies lyssavirus
RADDL	Regional Animal Disease Diagnostic Laboratory
RIG	Rabies Immunoglobulin
RNA	Ribonucleic acid
R0	Basic Reproductive Number
SIR	Susceptible – Infected – Recovered
SIRVQ	Susceptible – Infected – Recovered – Vaccinated – Quarantined

SISVQ	Susceptible – Infected – Susceptible – Vaccinated – Quarantined
STANDZ	Stop Transboundary Animal Diseases and Zoonoses
TRC	Thai Red Cross regimen
WAP	World Animal Protection
WHO	World Health Organization
ZMDH	Ziga Memorial District Hospital

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CHAPTER 1

An introduction to rabies and why it continues to persist

1.1 Rabies virus

The Rabies virus (RABV), the prototype species of the genus *Lyssavirus* in the family *Rhabdoviridae*, is a negative stranded, 200nm to 80nm long bullet-shaped RNA virus. Highly neurotropic in the infected host, it causes a nearly inevitable fatal encephalomyelitis once clinical signs occur – a disease commonly referred to as Rabies (Tordo et al., 1989; Wunner, 2007). While all warm-blooded animals are susceptible to rabies, there are only a few species in the orders *Carnivora*, *Chiroptera*, and *Primates* that can act as a reservoir and sustain a prolonged circulation of the virus in the population (Velasco-Villa et al., 2017). Whether the virus will become established in a population is likely determined by an interplay of ecological and genetic factors, but the exact drivers remain unclear (Hanlon et al., 2007; Mollentze et al., 2014)

Despite the fact that the molecular mechanisms of rabies transmission and the evolution of respective virus-host relationships may vary substantially between individual host species, the route and outcome of rabies transmission remains fairly conserved. Typically transmitted via animal bites (occasionally through scratches or licks at a site of wound or abrasion) through contact between saliva from infected individuals and ruptured skin or mucous membranes, the disease is almost unavoidably fatal after neurological symptoms have occurred.

Upon entering the body, rabies virions immediately begin to multiply in muscle tissues; however, due to an exceptionally strong immune evasion, the presence of the virus is not detected until the late stages of infection when clinical signs of pathological neuronal dysfunction announce the advent of an imminent death (Davis et al., 2015). This mechanism results in a relatively long asymptomatic incubation period during which the virus travels through peripheral nerves to the central nervous system in about 50 - 100 mm per day (Warrell and Warrell, 2004). The length of the incubation period is highly variable, and is

related to the site of exposure (i.e. distance to the central nervous system) and the viral dose administered during the infectious contact, with shorter incubation periods predicted by larger amounts of the virus entering the body (Kaplan et al., 1977). Smaller viral doses, on the other hand, lead to longer incubation periods, and in some cases potentially result in a complete abortion of the infection (Fisher et al., 2018). The absence of the host's adaptive immune response during the incubation period is both ironic and tragic, as when delivered in the vaccine form, RABV is highly immunogenic inducing reliable protective immunity (Fisher et al., 2018).

Once infecting the brain, the direction in which the virus migrates shifts outwards toward the salivary glands through which the host sheds the virus onto a new offspring case to reignite the transmission cycle. Whilst the final stage of rabies infection is characterized by an acute and fatal inflammation of the brain and spinal cord, the neurological symptoms take on two different forms. We traditionally associate rabies with what is called the "furious" or "excitative" form, characterized by outburst of aggression, whereas the "paralytic" form manifests as a rapid muscular degradation. However, these forms can alternate and the behavioural changes encompass more than just aggression or total paralysis, including sudden shifts in temperament, excessive affection, and difficulties breathing, eating and swallowing (Kaplan et al., 1977). To what extent one form dominates over another has been speculated to be due to the viral strain present in the body (Shuangshoti et al., 2016).

1.2 Rabies as zoonotic disease

Multiple strains of rabies virus exist. Each strain, a genetically distinct viral population, is exclusively maintained by a single reservoir host. Spillover infections, when a particular strain jumps onto a new host species, are possible, but usually short-lived without establishing a novel transmission cycle, even though several strains often circulate sympatrically (Mollentze et al., 2014). Such a phenomenon is likely due to a combination of physiological and ecological factors. Whilst phenotypic differences between rabies virus variants appear to be driven by strong host adaptation (i.e. homologous and heterologous strains result in differential disease progression and severity) (Hamir et al., 1996), ecological

settings ensure longer-term fidelity of the strain to its host (i.e. optimization to the host ecology underlying epidemiological parameters) (Mollentze et al., 2014).

Despite wildlife being the main host reservoir in most countries in the Global North, with vampire bat variants in South America, domestic dogs represent the primary cause of rabies infection in humans in places where rabies acts as a zoonosis (a disease transmitted from animal species to humans). Controlling rabies in wildlife has been documented with great success. For example, large scale implementation of oral rabies vaccination (ORV) across western and central parts of Europe resulted in elimination of wildlife mediated rabies from the red fox (*Vulpes vulpes*) after a sudden reintroduction of the virus into Europe and its subsequent outbreak in the 1970s (King et al., 2004). In North America, wildlife rabies continues to cause localized epizootic episodes mostly in racoons and skunks, but the number of human deaths due to infectious contact with wildlife falls between 0 and 3 cases annually (CDC, 2020). Sustained interruption of dog-mediated human rabies is, however, still to be achieved.

In low- and middle-income countries (LMICs) in Africa and Asia in particular, canine rabies (referred to as "rabies" from here onwards unless stated otherwise) results in a devastating toll in human lives and substantial economic costs. Despite lacking true pandemic potential, rabies has the highest case-fatality rate of any zoonosis, causing approximately 59,000 human deaths and costing 8.6 billion USD every year (Hampson et al., 2015). In addition to the threat to human lives and costs expended on post-exposure treatment and medical care, rabies imposes a major burden to livelihoods and food security, particularly in settings where smallholder livestock provides the primary means out of poverty. For example, losing a cow due to rabies can severely jeopardize a farmer's livelihood in most rural parts of Africa and Asia, leaving the victim without oftentimes the only financial means to seek healthcare in the event of exposure (farmers will usually attempt to protect their livestock by confronting the biting animal receiving bite injuries themselves) and leading to an enormous amount of stress, trauma and threat of death.

Despite its severity, rabies remains largely neglected. Like most zoonoses that are rampant nowadays, rabies is a disease of poverty. In most resource limited settings, rabies competes

with other diseases that are considered of higher economic importance for they directly affect agricultural species. Justifying the needs for funding is further hindered by often missing evidence of the extent to which rabies affects the local communities. Following an ongoing cycle of neglect, with no funding available for surveillance, insufficient or low-quality data undermine advocacy for more attention, while the terror of rabies imposed on already marginalized communities remains invisible (Cleaveland at al., 2014).

It is perhaps for the close relationship we have with dogs that, compared to its wildlife counterpart, canine rabies seems more erratic and challenging to control. Anthropogenic factors inherently shape dog spatial and population dynamics – such as changing the dogs' vital rates and social structures; manipulating the infected population; and relocating dogs, creating an everchanging network of metapopulations – and make it impossible for us to observe the system independently. For example, it has been shown that road networks strongly correlate with phylogenetic distance of the canine rabies virus, suggesting that human movement precipitates spatial patterns of rabies dispersal (Talbi et al., 2010; Brunker et al., 2015; Tohma et al., 2016). In fact, more broadly, it appears that historical long-distance movement of humans formed the contemporary distribution of canine rabies around the world (King et al., 2004). Dogs have been bred to human desires for centuries, and rabid dogs persecuted and culled since the times of Sumer (Tarantola, 2017).

Despite all the structural and logistical challenges, there are initiatives to bring attention to rabies and other zoonotic diseases and to secure sustainable support through interdisciplinary and transdisciplinary approaches, advocating for financial resources to be shared outside of the loss-making hierarchical structures (Cleaveland et al., 2014; Cleavland and Hampson, 2017). We have all the tools to eliminate rabies, but the strategic plans have yet to be realized.

1.3 Rabies control and elimination programmes

Rabies circulating in domestic dogs has been eliminated from the Global North, but it continues to persists throughout LMICs around the globe where it remains a major public health concern. Mass dog vaccination (MDV) is highly effective in reducing case incidence and leads to elimination of human deaths and interruption of rabies transmission at the

source in the dog population when delivered at scale and systematically for an extended period of time (Townsend et al., 2013, Ferguson et al., 2015).

The efficiency of vaccination campaigns largely depends on the spatial distribution of vaccine implementation, and the achieved and sustained coverage of immunized dogs. MDV campaigns are feasible across a wide range of settings, and current advances in knowledge and technology regarding vaccine storage outside the cold chain have made them even more widely accessible (Lankester et al., 2016, Lugelo et al., 2020). However, such campaigns must be undertaken annually, achieving >70% coverage homogenously across the landscape in order to maintain the critical level of immunity in the face of demographical losses and gradual roll-out (Coleman and Dye, 1996; Hampson et al., 2009; Townsend et al., 2013; Ferguson et al., 2015).

Such substantial efforts are often perceived as excessive in places where rabies competes with other pressing priorities. Short-lived vaccination campaigns and supplementary measures such as reactive vaccination or dog culling are then employed with irregular efforts, patchy results and/or limited evidence on their effectiveness. Consequently, the lack of comprehensive management leads to suboptimal results with damaging consequences. Unrealistic time frames of when elimination can be expected are commonplace, and rabies management activities such as active surveillance and post-vaccination monitoring are often overlooked or omitted completely in spite of the fundamental role that they play in evaluating the success of previous and planning of future vaccination campaigns (Purwo Suseno and Rysava et al., 2019).

In 2015 the Global Strategic Plan to prevent human deaths from dog-mediated rabies by 2030 was announced by the WHO (World Health Organization), OIE (World Organisation for Animal Health), and FAO (Food and Agriculture Organization of the United Nations) tripartite (with support of the Global Alliance for Rabies Control), setting a goal to eliminate dog-mediated rabies worldwide through “increased awareness, vaccinating dogs to prevent disease at its source, and life-saving post-bite treatment for people” in the next 15 years (WHO, 2018).

While rabies in dogs can be eliminated through mass vaccination campaigns, human deaths due to rabid bites are prevented by administrating post-exposure prophylaxis (PEP) upon exposure. These approaches work in parallel, and should be viewed with equal importance (WHO Rabies Modelling Consortium, 2019).

Accessibility and affordability of PEP is often cited as the main obstacle in reducing the number of human deaths from rabies (Hampson et al., 2016). This a particularly pressing issue in countries and communities with substantial inequalities in healthcare access, and little to no palliative care. Current changes in PEP administration protocols – switching from intermuscular to more efficient and cost-effective intradermal regimen – have made the vaccine more affordable at the national level, but it may not be a sufficient progress for individuals for whom the cost of seeking healthcare entails more than just the vaccine charge but also productive time lost during the health seeking behavior (in extreme but not rare cases travelling to clinics can take up to several days), travelling expenses, and often a difficult cultural choice between western medicine and traditional healing methods (Hampson et al., 2016; Amparo et al., 2018; Bihon et al., 2020).

On the other hand, in places where the personal cost of seeking healthcare is low coupled with poor level of rabies recognition due to minimal experience with the disease, PEP demands stay high despite a reduced incidence of rabies in dogs (Rysava et al., 2019, WHO modelling consortium, 2019). Whilst undoubtedly PEP decreases the mortality toll and should be made accessible to those at risk, in the absence of rabies control in the dog population, human deaths due to rabid exposures will continue to occur. Hence, there is a pressing need for more equitable strategies to prevent rabies in humans, including judicious use of PEP leading to redistribution of resources between public health and veterinary sectors, and protecting the communities by reducing the risk of exposure through dog vaccination and rigorous surveillance allowing timely identification of infectious dogs.

Rabies surveillance has been historically focused on methods based on passive sampling, with outdated guidance to test 0.01-0.02% of the estimated dog population (WHO, 2005). Such a small fraction of the population, however, precludes any success in detecting rabies given the notoriously low prevalence of the disease, further intensified by biased sampling

choices done either opportunistically or last minute in a spatially and temporally exclusive manner (Hampson et al., 2016).

The lack of formal surveillance then leads to a misleading representation of the disease with inadequate estimates of its magnitude, further exacerbating insufficient funding for control programmes, and late detection of rabies outbreaks long after extensive secondary transmission had been established within the area. Moreover, in places free from rabies or approaching the elimination goal, the risk of incursions prevents achievement and maintenance of rabies freedom and cannot be overcome without proficient diagnostic capacity (Tohma et al., 2016; Zinsstag et al., 2017, Rysava et al., 2020).

Limited laboratory capacity and infrastructure for rabies diagnostics combined with logistical constraints associated with sample recovery and submission leads to severe underreporting and absence of fundamental data on both rabies incidence in the dog population and, in some instances, human deaths (Scott et al., 2017). For example, in rabies endemic countries around Asia where PEP is more widely accessible, the lack of information on the infectious status of the biting dogs results in excessive expenditures on PEP, as a full course (2 doses in each deltoid administrated 4 times over 28 days) is recommended for true exposures and non-case patients indiscriminately, inevitably creating financial strains and vaccine shortages (Cleaveland et al., 2018; Rysava et al., 2019). On the other hand, in places where adherence to the health system is low, with no assessment of high-risk areas, vulnerable communities remain undetected leading to untreated exposures and unreported human deaths (Hampson et al., 2015; Taylor at al., 2017a).

Due to its high sensitivity and specificity, the fluorescent antibody test (FAT) is considered a gold-standard for rabies diagnostics (OIE, 2011). Its emphasis on notifiability and strong laboratory infrastructure, however, makes establishment of an effective and reactive surveillance system in resource limited settings difficult if not unachievable. Active surveillance based on clinical information of histories of biting animals provides an alternative. Triage of patients presenting at clinics for PEP treatment, followed up by investigations of suspicious incidents and contact-tracing of infectious individuals has the potential to increase rabies detection to >10% of dog cases (compared to the current

estimates of <5% case detection in most rabies endemic countries in Africa and Asia) (Hampson et al., 2016). In addition, more recent diagnostic techniques, such as field-based lateral flow devices that provide rapid results upon collection of brain tissue samples, can empower field workers to further engage with the surveillance process without depending on the centralized laboratory system and to react to field findings in a timely manner (Halliday et al., 2012).

Such integrated approaches not only have the potential to substantially increase case detection and early containment but also to strengthen the intersectoral relationships between public health and veterinary services that should be at the core of all zoonoses management programmes. A robust, responsive and ethical surveillance system is an essential part of successful elimination efforts; to serve as a control and a preventative measure to reduce the number and length of transmission chains in the dog population, precluding any undesired outbreak, as well as to guide policy decisions regarding public health practice.

Whilst active surveillance allows timely detection and removal of infectious individuals and appropriate allocation of PEP, post-vaccination monitoring of the dog population provides larger structural support to successful long-term delivery of MDV campaigns.

Post-vaccination surveys are critical for estimating vaccination coverage and dog population sizes to inform vaccine procurement and delivery in supplementary and subsequent campaigns. In most LMICs, the actual level of vaccine coverage falls far below reported values, which are often themselves already below the 70% threshold recommended to prevent rabies transmission. This stems predominantly from two logistical constraints: (1) without formal post-vaccination monitoring in place, coverage gaps remain unidentified and often aggravate over time, and (2) future vaccine procurement is based on repeatedly underestimated population sizes which then lead to insufficient stocks of vaccine available.

Conducting a formal dog population census is a rare practice in most rabies endemic countries, and often impractical as owners are either not required to or fail to register their dogs with relevant authorities. Instead, the usual policies for estimating dog population

sizes include extrapolation from a spatially homogeneous human to dog ratio (HDR) based on often outdated geographically or temporally singular data or a somewhat haphazardly derived ratio based on spatially limited field observations and general consensus among local authorities (Undurraga et al., 2017). In practice, this results in vaccine procurement solely based on an assumption that the dog population is a constant fraction of the human population with flat dog to human ratios applied across large administrative units.

Dog demography is, however, a complex process, reflecting spatial and temporal heterogeneity in birth and death rates due to variable pet management styles as well as mobility and other socio-cultural aspects of dog ownership rather than directly mirroring human population trends (Morters et al., 2014; Czupryna et al., 2016; Taylor et al., 2017). Hence, the missing information on the ecological background and demographic processes of the dog population creates further divergence between programmatic demands and expectations versus reality.

1.4 Modelling rabies

Analytical and modelling tools can help to explore the ways biological and ecological hypotheses relate to observed behaviours of the system, providing insights into and validation of mechanisms driving disease transmission, which in return can guide the development of intervention strategies and their adjustments as the targets shifts along the control implementation timeline.

The most effective policy on control strategies would be informed by local epidemiological dynamics. Uncertainty, however, hinders full understanding given data of variable quality and magnitude, and substantial heterogeneity in key parameters of rabies epidemiology and ecology.

Poor-quality surveillance data call for modelling techniques that can account for incomplete observations. So-called state-space models present a powerful approach to modelling the observation processes, but will yield more robust results for diseases that generally circulate at higher incidence (Beyer et al., 2010; Mollentze et al., 2014a).

Rabies spreads and increases in incidence slowly, mostly happening locally with occasionally erratic incidents causing focal outbreaks and incursions when prompted by connectivity links through landscape or human influence (Hampson et al., 2009; Townsend et al., 2013). A lot of debate has taken place around whether the disease is density or frequency dependent. Under the density-dependence paradigm, transmission would scale with dog densities. Such a trajectory has, however, not been observed, with the average number of secondary cases generated by each primary case consistently falling between 1 and 2, regardless of the geographic and demographic characteristics of dog communities studied (Morters et al., 2012). As such, rabies should be theoretically easy to eliminate with only ~17% of the dog population vaccinated. This assumption partly omits the effect of fast-paced demographic turnover on maintaining constant vaccination coverage through time, but more importantly the structured nature of contact patterns between dogs. At the same time, even frequency-dependent models of rabies offer inconsistent results as their assumption of homogenous mixing fails to reflect reality in which only a handful of susceptible dogs are usually available to infection at a time given the localized scale of rabies transmission.

Despite the ostensive complexity of the system, most existing models of rabies transmission simplify the role of stochasticity in the process of disease transmission and overlook potential implications of spatial heterogeneity and variability of critical epidemiological parameters shaping transmission (Coleman and Dye, 1996; Hampson et al., 2009). While for highly transmissible diseases individual/fine-scale differences can be largely ignored, for diseases with a lower transmission rate, such heterogeneities may have a major influence on the emergent dynamics of infection and can result in unpredictable outbreaks (Keeling and Rohani, 2008).

More complex, context-specific models that have been developed for canine rabies include individual based spatially explicit structures (Townsend et al., 2012; Dürr and Ward., 2015; Ferguson et al., 2015). These can, however, only simulate dynamics at a limited spatial scale, are largely intractable analytically and in terms of deriving generalizable results across settings, and prone to being malleable to the modeller's "desire".

Realistic, system-tailored models are required to capture the many idiosyncrasies of canine rabies such as heterogeneity in epidemiological parameters and environmental/socio-cultural settings, and the spatial patterns and scale of transmission. However, whilst built on an epidemiological and ecological backbone, such models should remain universal enough to generate consistent and robust results, as well as to provide straightforward guidance to evaluate and ensure progress towards elimination targets.

To date, modelling has provided many critical and often unintuitive insights into the epidemiology and control of rabies such as the need for high-coverage, spatially-comprehensive vaccination (despite the low transmissibility of rabies), and the ineffectiveness of dog culling (despite the popular belief that a reduction in population density will lead to a decrease in incidence) (Morters at al., 2012).

Although the observed long-term persistence of canine rabies remains an enigma, we are getting closer to a more holistic understanding of the system's complexity; high spatial connectivity and variability in the force and re-emergence of infection between settings, resulting from dogs' individual behaviour and inconsistent control efforts, likely play a critical role (Mancy et al., in prep). There is a multitude of empirical evidence that now needs to be explored and supported analytically, but a wealth of practical guidance on successful rabies control and management is at our fingertips waiting to be fully operationalized.

1.5 Thesis preamble

In the following chapters we will examine the theory and implementation of rabies control in Southeast Asia from three different angles. Chapter 2 will provide a unique overview of 10 years of rabies control and management in Bali, Indonesia. From a single case incursion to near elimination via an unexpected and devastating resurgence, we will analyse this unique dataset to draw insights from programmatic successes and failures along the journey, aiming to provide broader instructional support to other rabies endemic countries across the region. In Chapter 3, we will probe deeper into the advantages of enhanced surveillance and the operational issues associated with its implementation. Using a new surveillance design and mobile phone-based application developed for use at anti rabies

clinics in Albay province, Philippines, we will collect spatially refined data on patient bite incidence, PEP use and rabies cases in the dog population, and analyse them in the context of past and future risk of rabies exposure. The final chapter will then conclude with theoretical investigations in modelling of rabies dynamics, with a focus on supplementary control measures through dog quarantine. Here, we will build progressively more complex and realistic models, from basic ordinary differential equations to stochastic computational simulations, and evaluate dynamical changes and stability of rabies persistence under different management scenarios. Loosely parametrized on the data presented in the previous chapter, the primary objective for Chapter 4 is to offer a theoretical framework to assess the impact of supplementary measures to support MDV campaigns.

CHAPTER 2

Lessons for rabies control and elimination programmes – a decade of One Health experience from Bali, Indonesia

2.1 Background

Rabies is the archetypal One Health disease. Most human deaths result from dog-mediated transmission (WHO, 2013). Post-exposure prophylaxis (PEP) is highly effective in preventing the onset of rabies if delivered promptly after a person is bitten by a rabid animal, but in canine rabies-endemic countries many people die because access to PEP is limited. Mass dog vaccination can eliminate rabies from source populations (domestic dogs) but requires sustained effort and is not conducted systematically or at scale in most low- and middle-income countries (LMICs). Thus, although canine rabies is preventable, and has been eliminated in high-income countries, its neglect in LMICs means that it remains a major public health concern and economic burden.

International agencies are now advocating to eliminate dog-mediated rabies globally and to achieve zero human rabies deaths by 2030 (Abela-Ridder et al., 2016). As a result, efforts are being made to undertake large-scale mass dog vaccination programmes and to improve access to PEP. At the same time, incursions of dog-mediated rabies recorded around the world, highlight the risk that rabies poses as an emerging disease (Loke et al., 1998; Windiyaningsih, 2004; Tenzin et al., 2010; Vigilato et al., 2013). The emergence of rabies on the island Province of Bali, Indonesia in 2008 is a prime example. Although rabies has circulated in Indonesia since the 1880s (Ward, 2014), Bali had historically been rabies-free. Over the last decade the Indonesian government, together with related stakeholders, have undertaken control and prevention activities with the aim of re-securing rabies freedom. Here we report lessons learnt from these efforts and their applicability to other regions with endemic canine rabies and that are rabies-free but at risk from incursions.

When the first suspect human rabies case, a 4-year old child, was detected in Bali in September 2008, health authorities were ill-equipped to cope and there was no PEP on the island. The hope was that the outbreak could be confined to the Bukit Peninsula at the southern tip of Badung regency and that control efforts would prevent spread to the rest of the island (Fig. 2.1). Initial control efforts in late 2008 and early 2009 involved localized culling of dogs with strychnine (the majority of dogs in Bali are owned but free-roaming) and fixed-point vaccinations in the Bukit Peninsula. However, by late 2009 rabies had crossed the isthmus. Increasing incidence and animal welfare concerns led multiple stakeholders to become involved in the situation, including international agencies, local and international non-governmental organizations, and development/aid agencies in the region as well as the health, veterinary, legal and education sectors from local and national government. Ongoing control efforts have now reduced rabies incidence, but setbacks to complete interruption of virus transmission to achieve a rabies-free Bali have proven challenging. We review a decade of experience from Bali discussing insights for rabies control, surveillance and management in the context of the One Health approach.

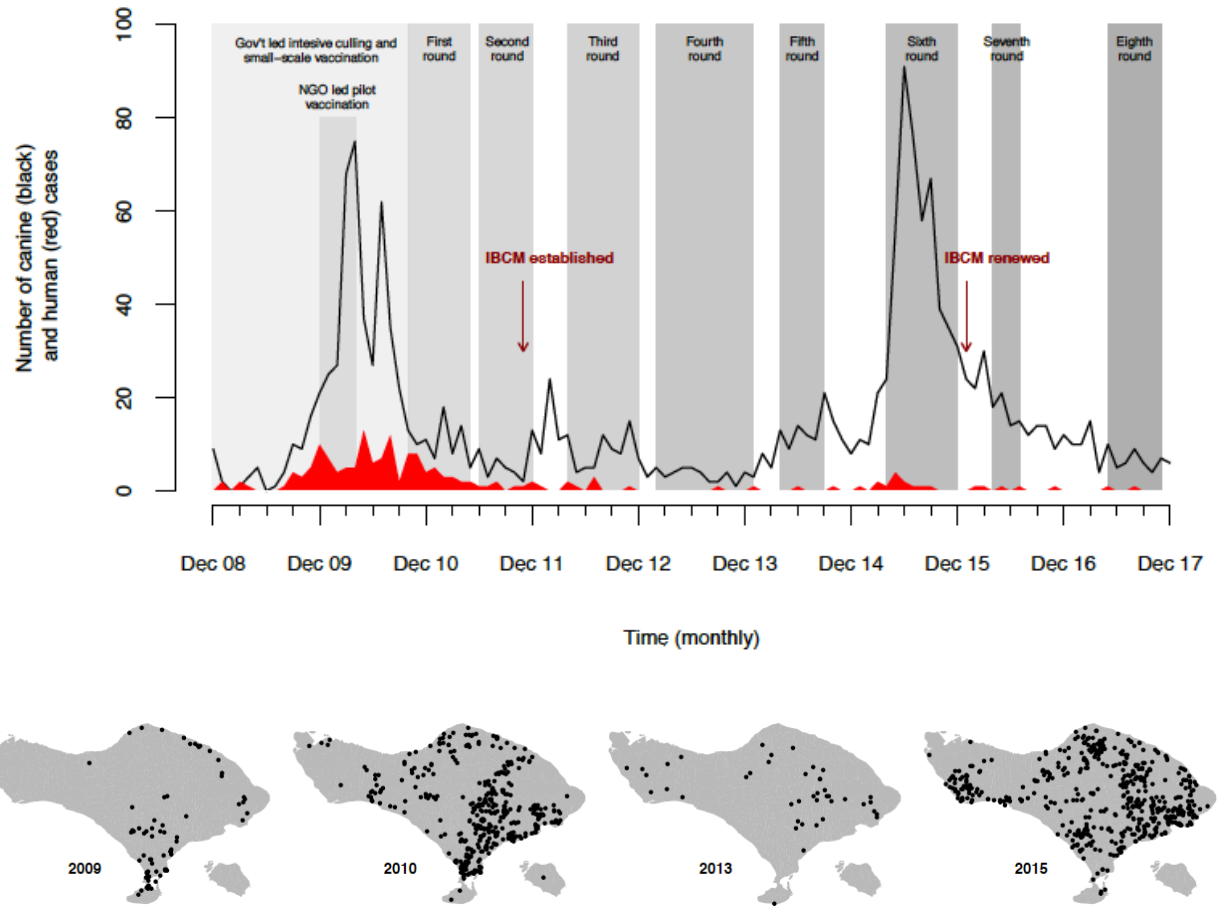

Figure 2.1: Rabies incidence in Bali since December 2008 until December 2017. Confirmed dog rabies cases (black line) and human rabies deaths (red polygon) with grey shading showing the timing of dog vaccination campaigns; different vaccines were used during this period. Culling of unconfined dogs was most intensely conducted at the beginning of the epidemic. In response to international pressure, culling was officially suspended in 2011, but has not been completely discontinued to date. In autumn 2015, the Balinese government supported targeted culling of dogs in reaction to the second outbreak. Integrated bite case management (IBCM) was established in late 2011, but, in spite of improved case detection, was not maintained. IBCM was re-introduced in late 2015. Maps illustrate the location of cases in the years following the outbreak; in 2009 when the spatial spread of rabies from the Bukit peninsula was evident, and in 2010 when rabies was widely distributed. By 2013, many fewer cases were detected in foci across the island, but rabies subsequently re-emerged in 2014-15 with occurrences throughout Bali.

2.2 Control strategies

The main approach recommended for the control of rabies in dog populations is mass vaccination (WHO, 2018a). Dog population management activities are also conducted with the intention of controlling rabies (Taylor et al., 2017), and culling of dogs is often the first response taken to outbreaks in LMICs. When rabies was first detected on Bali, there were several challenges to implementation of effective control measures. Vaccination of dogs was illegal and perceptions of an excessively large dog population contributed to culling being implemented as the first response by local government. Dog vaccines were, however, soon brought to Bali and local people advised to bring their dogs to central point locations on the outbreak-affected peninsula where government staff vaccinated their dogs. Vaccines produced in Indonesia (Rabivet Supra 92) were used at this time. However, these were less effective for mass vaccination campaigns compared to vaccines recommended by the World Organization for Animal Health (OIE) as they required a re-vaccination booster after three months to generate an acceptable level of immunity. Although over 90% of dogs on Bali are owned, they are mostly free-roaming and not easily brought to vaccination stations. Lack of coordination also sometimes led to culling of vaccinated dogs (although dog vaccinations were recorded, vaccinated dogs were not marked and culling was undertaken with haste). Owners also quickly replaced their dogs that had been killed, usually with unvaccinated puppies and dogs brought from elsewhere, further risking importation of rabies. The

confluence of these factors meant that only low and short-lived vaccination coverage was achieved, and by mid-2010 rabies had spread across the entire island (Putra et al., 2013).

In response to these difficulties, the Bali Animal Welfare Association (BAWA) developed a technique for vaccinating dogs using trained dog catchers equipped with nets (Townsend, 2013). From December 2009 to September 2010, four teams of six persons (four dog catchers, one vaccinator, one recorder), carried out door-to-door vaccination throughout neighbouring Gianyar and Bangli regencies, using long-lasting vaccines donated by the Australian Government. Coloured collars were used to mark dogs at the time of vaccination, and post-vaccination surveys conducted on consecutive days following campaigns, counting marked (vaccinated) and unmarked dogs. In 10 months, the four teams vaccinated over 73,000 dogs in the two regencies with coverage estimated to exceed 70% in almost all banjars (sub-villages). BAWA's proven approach, that high coverage could be reliably achieved and monitored even in areas with high densities of unconfined dogs, was adopted. Local and international stakeholders including BAWA, Balinese provincial government and World Animal Protection (WAP, formerly World Society for Protection of Animals) planned the first island-wide mass dog vaccination, and from October 2010 to April 2011 over 70% of dogs were vaccinated in most banjars across the island (Fig. 2.1). Since 2011 island-wide vaccinations have been conducted annually by the Balinese government with technical and operational support from the Food and Agriculture Organization (FAO). To date, 31 teams of dog catchers have been trained providing capacity for large numbers of dogs to be rapidly vaccinated. During 2015 and 2016, improvements in these techniques for catching and handling of unconfined dogs were developed and competitions between the teams were intensified to increase engagement in and impact of vaccination campaigns.

In addition to vaccination activities, control strategies aiming to reduce the dog population were carried out with varying intensity and sub-optimal results. Dog culling, implemented primarily through strychnine darting, was officially advised against by local and international welfare groups. The first island-wide mass vaccination campaign in late 2010 was supported by BAWA and WAP under an agreement that culling would be discontinued. However, some dog culling was conducted in response to reports of human and animal rabies deaths as demanded by communities, and sometimes in localities where the government considered

the dog population to be too large. Culling was also frequently opposed by local communities and many people complained when their owned and often vaccinated dogs were killed during culls. Ultimately, culling did not contain rabies spread. In contrast, it was likely counterproductive as dogs were moved to avoid culls, possibly transporting dogs with latent rabies. The rate at which rabies reached all regencies of Bali, including the island of Nusa Penida indicated involvement of human-mediated transport in rabies spread, in addition to the running behaviour of infectious dogs (Townsend, 2013). Moreover, evidence demonstrates that rabies transmission is largely independent of population density, hence approaches based on reducing the dog population will not control rabies (Townsend, 2013). As a result, the national policy in Indonesia now officially condemns indiscriminate culling and recommends selective and targeted euthanasia of suspect rabid dogs for rabies control.

Although mass dog vaccination strategies successfully controlled rabies on Bali following the first epidemic and subsequent re-emergence, the long-term goal of achieving rabies freedom has yet to be accomplished. To achieve rabies freedom requires sustained effort and commitment; even when incidence is declining, coverage must be maintained with mass vaccinations continued for at least two years following six consecutive months with no detected cases (Townsend, 2013). Yet, reduced rabies incidence on Bali led to a false sense of security. Island-wide mass vaccination is a substantial logistical and financial undertaking, and changes in vaccine procurement and roll-out disrupt the program's success. For instance, a new vaccine was used for the annual vaccination campaign in 2014, but only following resurgence of rabies in 2015 (Fig. 2.1) did the relative efficacy of different vaccines became apparent (Fig. 2.2). Measures were taken to improve subsequent campaigns, first and foremost through procurement of high-quality vaccines for use during the sixth campaign in 2015. Supplementary vaccinations were also conducted immediately after the main campaign targeting puppies, free-roaming dogs, and unvaccinated dogs and were completed in villages where coverage was estimated to be less than 70%. In addition, reactive vaccinations were completed in areas with most detected cases.

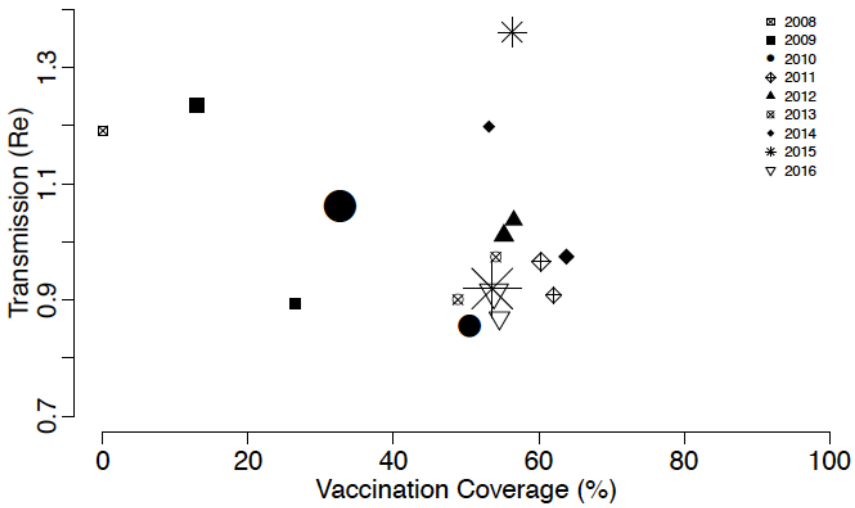

Figure 2.2: The influence of vaccine type and vaccination coverage on rabies transmission. Relationship between mean vaccination coverage (%) and the effective reproductive number, R_e. Vaccination coverage was projected using data on vaccination campaigns and assumed to wane with demographic turnover of the dog population and vaccine longevity (Townsend, 2013). R_e was estimated as the average number of secondary cases generated by each primary case, from the construction of 1000 bootstrapped transmission trees, following previously described methods (Hampson et al., 2009). Individual estimates of R_e and local vaccination coverage (both at the site of each rabies case) were averaged across six-month time windows, with symbols indicating the year of each six-month estimate and scaled by the number of cases contributing to the estimate (17 data points in total, from the second half of 2008 until the end of 2016). There was a strong negative relationship between transmission and vaccination coverage based on a weighted linear regression after removal of the outlier from the first half of 2015 during the aftermath following use of the ineffective vaccine (regression coefficient=-0.005, p-value=0.005, R-squared=0.39).

These challenges highlight the long-term nature of disease elimination programmes and the difficulties in sustaining control efforts during the endgame. A relaxation or failure of control measures can considerably set back progress, but maintaining financial commitment and motivation of personnel to undertake such extensive operations is difficult. Long-term planning required for elimination must include budgeting for high-quality vaccines with procedures in place to prevent delays in securing vaccine and delivery to the field. Monitoring and surveillance, including good data management, is also necessary to ensure progress is on track. Although conducted only intermittently over the 10-year period (in 2010, 2011, and 2016), post-vaccination transects were essential in estimating vaccination

coverage and dog population sizes on Bali, directly informing vaccine procurement and delivery plans. Political buy-in and increased public awareness are crucial for vaccination campaigns to be conducted in all communities, as is micro-planning and post-vaccination monitoring to ensure this is achieved. Modelling work motivated by the lack of engagement by one of the regencies on Bali prior to the first island-wide vaccinations demonstrated that unvaccinated communities jeopardise prospects for achieving rabies freedom (Townsend, 2013).

2.3 Surveillance

The lack of formal surveillance for rabies (both in humans and animals) on Bali and the ban on dog vaccination prior to rabies emergence in 2008 contributed to the relatively late detection of disease, at which point substantial secondary transmission had already occurred within the dog population. Had rabies been detected and effective control measures enacted earlier, it is likely that the disease could have been contained without causing such major public health and economic impacts (Townsend et al., 2012). Rabies was only suspected to be circulating in Bali after unusual encephalitis fatalities were reported from the Bukit peninsula (Fig. 2.1). The Australian government supported the re-establishment of the direct fluorescent antibody test, the gold standard for rabies diagnosis, at the regional disease investigation centre (DIC) in Denpasar. From this point on the DIC conducted laboratory surveillance for the province. In line with outdated recommendations to sample 0.02% of the dog population for rabies surveillance (WHO, 2005), large numbers of indiscriminately culled animals were tested for rabies at considerable expense. Efforts were subsequently made to target surveillance, and integrated bite case management (IBCM) was introduced whereby veterinary officers investigated suspect biting animals following incidents reported by bite victims, which significantly improved case detection (Fig. 2.1). However, IBCM was not maintained and case detection declined, possibly giving the sense that rabies was under control. Following re-emergence in 2014–15, IBCM was reintroduced with refresher training provided to personnel, and case detection again increased.

Surveillance data from the last ten years provide valuable insights that can inform rabies control. Initially cases were detected only in the Bukit peninsula suggesting a point source

introduction (Fig. 2.1). This was subsequently confirmed from genetic characterization. Viruses on Bali were related to those previously circulating in Kalimantan and Sulawesi, and it is thought that fishermen inadvertently brought a latently infected dog to Bali although the source of the outbreak has not been pinpointed (Muhardika et al., 2014; Dibia, 2015). Human-mediated movement was shown to play a significant role in the early spread of the disease (Townsend, 2013), but the spatiotemporal pattern of cases in subsequent years show that local movement of rabid dogs was responsible for the vast majority of transmission. These patterns did not reveal any environmental or population variables predictive of rabies transmission, only that new cases were strongly associated with recent nearby cases (Fig. 2.3). Nonetheless, this finding has important management implications. If cases can be detected and response measures enacted rapidly they can stem local transmission, but vaccinations must be conducted rapidly and over a sufficiently wide radius otherwise disease will continue to circulate unabated beyond the area of control.

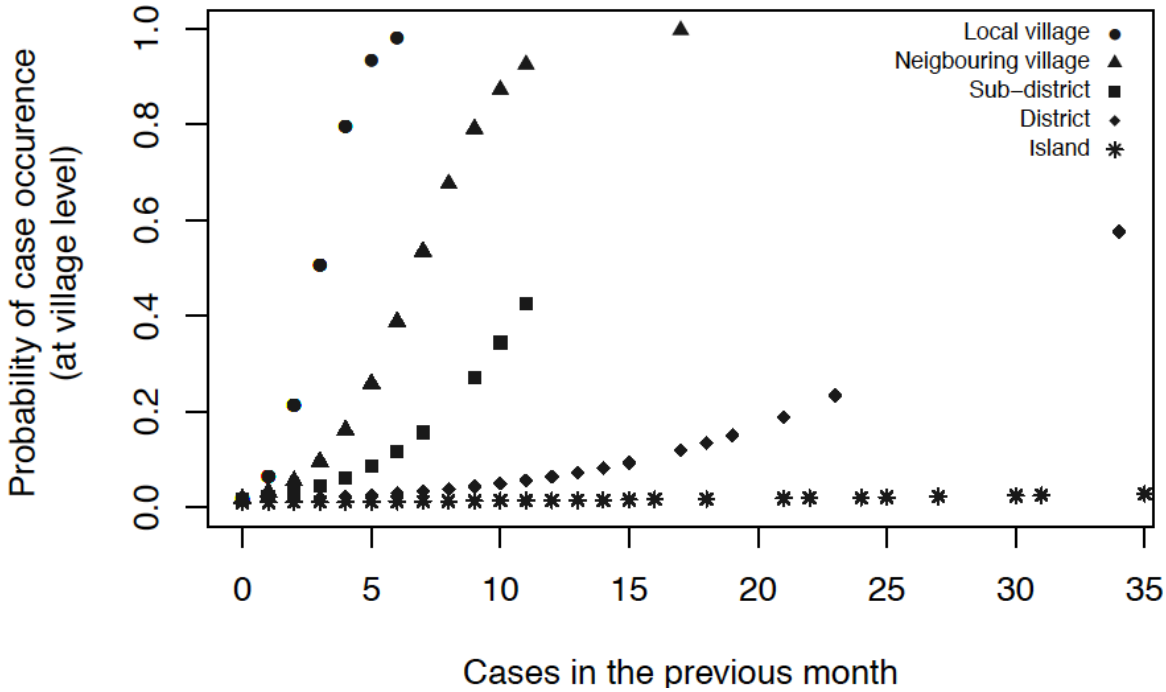

Figure 2.3: The influence of recent rabies cases on future rabies occurrence at different spatial scales. Fitted relationship between cases detected in the previous month at the specified spatial scale (x axis, point-typed) and probability of observing cases in the focal village in the current month (y axis).

Detection of cases through effective surveillance is critical to maintaining commitment to control efforts. If surveillance is targeted and effective, then declines in detected cases mark the impact of successful control measures. But if surveillance lapses, declines in cases will be falsely attributed to successful rabies control. Care must therefore be taken in communicating messages about progress from surveillance data, and in all circumstances, emphasis should be placed on not discontinuing control measures prematurely. Indeed, case detection should be used to emphasize the continuing need for vaccination until an area can be declared free from disease. In the case of rabies, dog bites by suspicious animals are a highly sensitive sentinel for the presence of rabies (Hampson et al., 2017). A One Health approach including close collaboration and sharing of information between the veterinary, medical, and public health sectors is therefore vital for improving case detection and is key towards rabies prevention and control (Fig. 2.4).

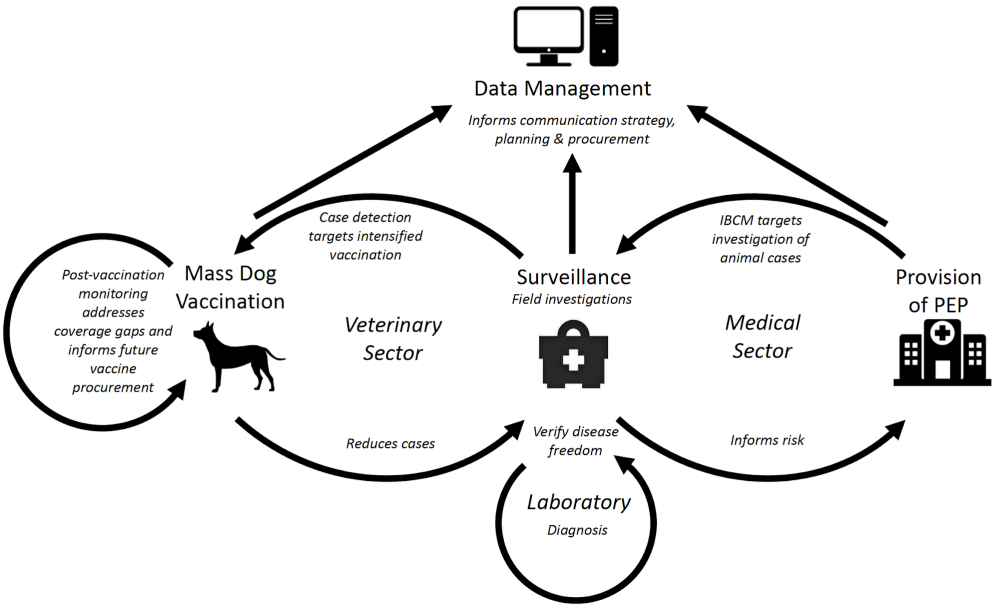

Figure 2.4: Schematic illustrating a One Health approach for a rabies elimination programme. The medical and veterinary sectors have key responsibilities for provision of PEP and mass dog vaccination respectively, that directly impact their corresponding intersectoral partner. Integrated surveillance (interactively informed by both public and animal health sectors) is at the intersection of all activities: it is used to monitor progress and inform management actions including procurement of human and animal vaccines. Use of integrated bite case management (IBCM), whereby identification of suspicious animal bites informs investigations, is a direct channel of communication across sectors and is a sensitive method to enhance surveillance to verify freedom from disease and for rapid outbreak response in areas at risk of incursions.

Table 2.1: Recommendations drawn from the rabies control programme on Bali.

Surveillance – routine animal surveillance on Bali detects only a small fraction of circulating cases in the dog population (<10%). Indiscriminate dog culling on the pretext of surveillance (laboratory testing of culled animals) is not effective for detecting rabies. In contrast, surveillance, coupled with increased public awareness, targeted through integrated bite case management (IBCM) is a sensitive and efficient way to increase case detection. Once reduced to low levels (an average of <10 canine cases detected per month through routine surveillance), effort should be made to enhance surveillance. Using IBCM, follow-up of high-risk bites is expected to detect 20-40% of probable rabid dogs and sample recovery from investigations should at least double the number of confirmed canine cases compared to routine surveillance (Undurragga et al., 2017; Rajeev et al., 2018).

Vaccination – comprehensive island-wide mass campaigns should be conducted annually in all villages, aiming to achieve high coverage (>70% across all areas, including sub-villages and remote settlements). At least two years of mass dog vaccination should be undertaken without any case detection under surveillance enhanced by IBCM as part of procedures to verify freedom from disease, before discontinuation of mass dog vaccination can be safely undertaken (WHO, 2018a). Supplementary vaccinations should target puppies born after campaigns and unvaccinated dogs missed during campaigns. Emergency response vaccinations should be guided by IBCM, implemented rapidly (<10 days since case detection) and cover an extended radius, for example villages within ~10km radius of the detected case.

Vaccines should be of high quality – quality vaccines are those that have sufficient appropriate antigenic content to produce rapid and long-lasting immunity in vaccinated animals with one application. Vaccines that require boosters greatly increase the effort and cost required to achieve sufficient coverage. Revaccination of dogs after short periods is logistically more challenging and very expensive. Moreover, trust is often lost in vaccination programmes as a result of adverse effects that can follow from the use of poor-quality vaccines.

Planning is required to ensure that there are no legal, logistical and financial constraints to implementing rapid response vaccinations. This should include advance planning to ensure the supply of internationally recognized vaccines from recommended suppliers for the duration of the programme, factoring in intensified vaccinations as freedom is approached, and continued vaccinations for two years after the last detected case to verify freedom from disease.

Appropriate delivery strategies are needed that can reach the vast majority of the dog population. It only became evident following initial local government vaccinations carried out at central points that most dogs would not be reached in this way in Bali. The use of trained dog catchers with nets has now been tested extensively in Bali and shown to be very effective. This approach should also be considered for use in other settings where patterns of dog ownership are similar to Bali. International organizations now have built up technical expertise in this approach which should be sought as required.

Monitoring – vaccinated dogs should be identified using long-lasting durable collars to facilitate identification during post-vaccination surveys to identify areas with low coverage, and the numbers of dogs vaccinated should be compared with previous campaigns to further check performance. Collars on

vaccinated dogs directly facilitate targeted supplementary vaccinations and emergency response vaccinations and should be promoted through responsible dog ownership.

Culling dogs is not recommended – it is not only inhumane, but also ineffective for rabies control. Specifically, dog owners often move their dogs to avoid culls, or bring in unvaccinated dogs from elsewhere to replace their animals that have been culled. This increased human-mediated movement risks spreading rabies. Culling also creates tensions between local communities and government and can reduce engagement and participation in more effective strategies such as dog vaccination. Moreover, the population quickly returns to pre-cull levels, leaving culling ineffective even as a dog population management tool.

Dog population management strategies should be implemented to encourage responsible dog ownership with a focus on vaccinating dogs, particularly puppies to maintain high levels of coverage.

Communication between stakeholders, across the veterinary and medical sectors including public health personnel, animal health officers, epidemiologists and laboratory technicians conducting surveillance activities, to the media, the local public and high-level donors are vital for maintaining engagement and support for ongoing control measures. Communications should be frequent and guided by surveillance information, with a focus on communicating effective strategies to overcome misinformation, which is likely to circulate during emergency situations and should adopt a realistic timeframe of when elimination goals can be achieved.

2.4 Management and coordination

Success of rabies control programmes is often hindered by limited community engagement and misconceptions about rabies, with a disconnect between research, policy and implementation. Bali offers an interesting and complicated story on the evolution of multi-partner and multisectoral collaboration for disease control, highlighting practices necessary to bridge this gap.

The lack of surveillance and subsequent effective control measures at the time of the incursion led to this tragic and costly situation. Resources were limited at the onset of the outbreak when investments were required to set up surveillance and control measures. Likewise, towards the end of the epidemic when cases were declining, reduced investment and prioritization of the control programme reflected fatigue and under-budgeting. At such times, planning of rabies interventions is made under enormous pressure and often with limited prior experience. For example, until the outbreak, vaccines were incorrectly believed to cause rabies rather than prevent it, and culling seemed to many stakeholders to be a more intuitive strategy to combat rabies given the large population of free-roaming dogs on

Bali. Technical support is therefore invaluable to ensure the effective planning and implementation of control measures in outbreak situations and to support the objective of elimination. Further modelling on the effectiveness of control activities and their optimization would greatly benefit Bali and other communities facing these dilemmas.

One of the most useful lessons learnt from the response to rabies in Bali is the importance of partnership and effective communication across the many stakeholders, high-level government policy makers, and donors. The dramatic decline in rabies incidence in late 2010 resulted from coordination of resources and capacity rapidly learnt from pilot activities. Whilst donations of long-lasting vaccines from the Australian Government initiated the process, successful implementation would not have been possible without the technical efforts and capacity building provided by in-country partners. Manpower and operational funds for training and administration of vaccines were initially considered a severe limitation. However, BAWA generated evidence to show that large numbers of free-roaming dogs could be vaccinated rapidly and this led to further support from local and national government, and technical assistance projects implemented with government by international organizations such as FAO. Nonetheless, misperceptions still had to be overcome and persuading some local stakeholders of the need to vaccinate in all communities was critical (Putra at al., 2013). Data management systems and technical support with data analysis from FAO have continued to play a key role in engaging governmental partners and supporting local implementation. Managing and coordinating across donors and partners was in itself a challenge, particularly given the political sensitivities associated with control mishaps and differing cultures and understandings of rabies and its control.

Whilst multi-partner relations generated positive outputs, intersectoral collaboration remains challenging. Limited infrastructure and communication between human health and veterinary workers hindered surveillance at the start of the outbreak, and except when IBCM was implemented, investigations of animal and human rabies cases were undertaken independently. Strong communication and shared responsibilities between all relevant sectors are, however, imperative to effective rabies control and prevention (Fig. 2.4). Targeted surveillance of rabies suspect dogs identified through dog-bite patients facilitates

detection of animal cases and leads to more appropriate PEP recommendations, thereby reducing associated economic costs (Hampson et al., 2016; Lechenne et al., 2017; Undurraga et al., 2017a; Rajeev et al., 2019; Rysava et al., 2019). Successful rabies control in dogs directly benefits human health. Therefore, the One Health approach rooted in effective intersectoral and transdisciplinary partnerships and communication is key to rabies elimination efforts, and as such, rabies provides a testbed system for other zoonotic diseases.

Successful rabies control programmes require engaging communities and stakeholders and implementing culturally acceptable and effective control activities. Misconceptions about rabies often lead to counter-productive actions and reduced participation. As a result of the resurgence of rabies in 2015, hard won confidence in vaccination programmes was lost, and some politicians promoted culling as an alternative, claiming it would be cheaper than more dog vaccinations. While subsequent island-wide dog vaccinations have brought rabies back under control, poor intervention choices had damaging and extremely costly implications – likely setting back Bali's prospects of achieving rabies freedom by at least five years. Outreach programmes are essential to achieving and maintaining buy-in and should, thereby, focus upon educating communities on rabies risk and available control and prevention measures. Between December 2016 and April 2017, FAO conducted a pilot study in Pejeng village, Gianyar regency aimed at increasing community compliance with rabies control through a series of educational workshops and local law enforcement for responsible dog ownership facilitated by village health workers. Results provide optimism that actions taken locally can lead to increased public engagement and awareness of rabies risk in the community, whilst fostering daily dialogue between veterinary and health personnel.

Elimination of rabies is achievable if long-term commitment to effective control strategies and surveillance is sustained. The time to complete interruption of rabies virus transmission and declaration of freedom is typically longer than anticipated by both politicians and academics, often because delivering surveillance and control activities in practice at scale in all communities is much harder than it might appear. Therefore, maintaining momentum when cases are declining is important, with government needing to commit sufficient

resources and not disengage prematurely. Communication strategies must stress this need for sustained effort and manage expectations about the time and investment required - for practitioners and high-level stakeholders. Misinformation poses a major threat to the control of rabies in an emergency situation and can compromise achievements when progress has been made and elimination is approached. Development of a coordinated communication strategy involving all relevant sectors is therefore a key component of control efforts to make rabies-free Bali a reality and prevent further spread of rabies across Southeast Asia.

2.5 Conclusion

Development and implementation of control options for rabies require careful consideration of the availability of resources as well stakeholders' engagement and support to carry out interventions. Given financial, technical and structural constraints in LMICs, it is important to identify the most appropriate strategies and allocate resources accordingly. To eliminate rabies from Bali will require time and commitment; efforts should be directed towards well-coordinated high coverage annual dog vaccination campaigns using a high-quality vaccines and enhanced surveillance instead of ineffective activities, such as dog culling, and indiscriminate sampling of apparently healthy animals for surveillance. The isolated nature of Bali, an island, makes it an ideal target for achieving freedom from rabies, but the logistics of vaccinating the large numbers of mostly free-roaming dogs also makes it challenging. Lessons drawn from Bali (Table 2.1) are applicable to other large and dense populations, where dog management and rabies control may appear overwhelmingly difficult. To achieve rabies elimination on Bali, a One Health approach including the combination of appropriate technical training and continuous efforts to ensure engagement and awareness, with multisectoral support from both governmental and non-governmental partners have demonstrated that promising results can be achieved if, partnerships, political will, and local and national commitment are cultivated.

CHAPTER 3

One Health surveillance model – a case study of Integrated Bite Case Management (IBCM) in Albay province, Philippines

3.1 Introduction

Canine rabies has been eliminated across the Global North, but throughout the majority of low- and middle-income countries (LMICs), the disease remains a serious public health concern and economic burden. Every year, thousands of people die and billions of dollars are lost owing to rabies spread by domestic dogs (Hampson et al., 2015). Although fatal once clinical symptoms appear, rabies is preventable upon prompt administration of post-exposure vaccinations after a person is bitten by a rabid animal and can be controlled in the source population through mass dog vaccination (Rysava et al., 2019). Post-exposure prophylaxis (PEP) is highly effective in preventing human deaths but its repeated shortages, high costs and typically limited awareness of rabies in remote communities leave many people at risk without access to appropriate treatment. Mass dog vaccination can eliminate rabies from the dog population, preventing further transmission to humans, but requires a sustained effort and is not conducted systematically or at scale in most LMICs (Hampson et al., 2015).

In the Philippines, rabies control efforts are being implemented in order to reduce infection rates, but only a few islands and provinces are on track for elimination of both human and dog rabies (Miranda et al., 2017; Barroga et al., 2018). Despite ongoing initiatives by the Philippines national government to prevent zoonotic rabies transmission, canine rabies remains a major concern in the public health sector across the country, with 200-300 people dying from the disease every year (Rysava et al., 2019). With rabies awareness elevated through anti-rabies initiatives and presence of human deaths as a consequence of the disease, PEP demand increases at a rapid rate. As a result, local and national healthcare budgets can be strained with indiscriminately administered PEP, eventually redirecting focus from essential mass dog vaccination campaigns whilst not necessarily reflecting the actual rabies incidence in dogs.

A major impediment to understanding local dynamics and controlling the disease effectively lies in relatively sparse and low-level detection in the reservoir dog population - with estimates suggesting that less than 10% of canine infection is being reported (Townsend et al., 2013; Hampson et al., 2016). Lack of integration between human and animal health sectors significantly limits the quality of surveillance; suspect dogs that could be rapidly identified and isolated through investigating animal bite incidents are often not followed up on and dog samples are recovered only in the event of human death. Detection of rabies fully relies on routine surveillance; identified animals are killed and samples are tested using the fluorescent antibody test (FAT). This approach is largely ineffective given the overall low prevalence of rabies combined with low sample size required (0.01% - 0.02% of the total estimated dog population [WHO, 2005]), and the often spatially and temporarily clustered, opportunistic sampling effort (Hampson et al., 2016). Moreover, even identified rabid animals are not always reported in a timely manner or available for sampling, and diagnostic capacity is limited in some settings (WHO, 2015).

In contrast, active case-finding by tracing of dog-bite patients attending Animal Bite Treatment Centres (ABTCs) can lead to enhanced surveillance sensitivity (Hampson et al., 2016; Rysava et al., 2019). Histories of biting animals provide valuable and oftentimes the only epidemiological information to inform rabies management. Clinical information can also provide a better measure of disease incidence than laboratory confirmed cases, depending on the level of in-country capacity and routine surveillance, and guide field investigations of rabies suspect incidents. Such integrated approaches using bite patients as sentinels for rabid dogs have the potential to substantially increase case detection and early containment, while at the same time strengthen intersectoral relationships between public health and veterinary services.

This study is underpinned by the development and implementation of an integrated, intersectoral surveillance scheme to consolidate human and animal health sectors to guide field investigations in response to animal bite incidents. Here we developed detailed epidemiological questionnaires recorded using a mobile phone application at three ABTCs in Albay province, Philippines to document bite case histories, and to inform and trigger field investigations where appropriate.

Our primary objective was to critically evaluate the utility of existing and proposed routes of rabies surveillance. The first aim was to identify and pilot surveillance criteria for discerning bite exposures to guide field investigations for timely detection and containment of rabies highly suspect dogs. Secondly, we used the information collected through this surveillance scheme to assess whether dog cases classified as "rabies highly suspect" offer a more suitable alternative for detection of rabies in the dog population compared to the routine surveillance conducted at "random" or surveillance estimates extrapolated from human bite reports. Specifically, we examined whether the reported bite incidence of patients presenting at clinics corresponds with the actual rabies burden in the province. Ultimately, we further employed the bite history data to establish their potential to provide any insights into where positive cases can be expected in the future in the context of vaccination coverage and previous rabies presence in the area.

3.2 Methods

3.2.1 Study site

We established a 13-month longitudinal study of dog bite-injury patients beginning in March 2018 in Albay province, in central Bicol peninsula (Region V, Philippines). The province comprises 19 municipalities and had a reported population of 1,314,826 in 2015 (Philippine Statistics Authority, 2016). As surveillance detects only a minor fraction of transmission events, it is difficult to estimate the true incidence of rabies across the dog population. Rabies in the province likely persists at a low-level of endemicity with frequent incursions from neighbouring provinces and nearby islands. Vaccination campaigns have been conducted since 2013 at different spatial and temporal scales. Between 2015 and 2016 annual vaccination campaigns were temporarily strengthened as part of the OIE STANDZ (World Organisation for Animal Health Stop Transboundary Animal Diseases and Zoonoses) project (OIE, 2016; Barroga at al., 2018). However, the subsequent vaccination campaigns have become less comprehensive and more spatially heterogeneous with some barangays (villages) omitted completely in certain years.

3.2.2 PEP and rabies immunoglobulin provision

Both vaccines and rabies immunoglobulin (RIG) are provided free-of-charge from government-run animal bite treatment centers located within hospitals and can also be

bought privately from Animal Bite Clinics (ABCs). ABTCs administer vaccines intradermally (ID) following the updated Thai Red Cross regimen (TRC) with two 0.1ml doses (to deltoids) delivered on day 0, 3, 7 and on some occasions on day 28 (patients are charged for the fourth dose). Following the WHO guidelines, RIG should be provided to all Category III patients, directly into and around the wound and as soon as possible after the exposure. The exact dose depends on the weight of the patient, with approximately 2 ml (equals to one vial) of RIG required per 10 kg (WHO, 2014). There are three government-run ABTCs in the province located at Bicol Regional Training and Teaching Hospital (BRTTH), Legazpi City, Josefina Belmonte Duran Memorial District Hospital (JBDMDH), Ligao City and Ziga Memorial District Hospital (ZMDH), Tabaco City (Fig. 3.3a). The only private clinic in Albay is located in Daraga, a short distance from Legazpi City.

3.2.3 Bite patient interviews and follow-up

For the duration of this study, from 1 March 2018 to 31 March 2019, one data collector was permanently stationed at each of the three ABTCs. The ABC in Daraga was excluded from the study due to a negligible patient throughput. Nurse personnel at clinics recorded patient background information including each patient's name, address and phone number within their standardized animal bite registry books. Collected information was then shared with the study data collectors who conducted a short interview with patients after PEP was administered. During the interviews the data collectors inspected bite incident background, history and health condition of the biting dog and details on the exposure and treatment (Interview Forms S3.1 and Investigation Guidelines S3.2). All patients were required to quarantine and observe the biting dog for a 14-day period directly if the patient was the dog's owner or to contact the dog owner to follow the same protocol. Additionally, bite patients/responsible dog owners were urged to immediately contact the interviewing data collector should any behavioural/symptomatic changes occur in the quarantined animal. Otherwise, when telephone numbers were provided, bite victims were called after 14 days, and a follow-up questionnaire was completed over the phone to identify whether an incident involved a potentially rabid animal. Criteria used were that the animal was either sick, exhibited unusual aggressive behaviour, it had bitten multiple people or other animals, had been killed, died or was untraceable during the 14 days following the bite. If these criteria were met (and reported at any point during the 14-day period), the bite was

suspected to be due to a rabid animal and a field investigation was prompted by contacting a corresponding Local Governmental Unit (LGU) officer. If the suspect animal was found sick or dead, the animal head/brain sample was collected for direct Fluorescent Antibody Test and sent to the Regional Animal Disease Diagnostic Laboratory (RADDL) of the Department of Agriculture Bicol in Cabangan, Camalig (municipality in Albay) to obtain laboratory confirmed diagnosis. Conversely, government-led routine field investigations were only conducted if a human death occurred with no respect to or knowledge of the incriminated bite histories (Department of Health, 2012). Ethical approval for the study was granted both locally by the Institutional Review Board at the BRTTH, overseen by the Philippine Health Research Ethics Board (PHREB), and in the UK by the Biomedical and Scientific Research Ethics Committee (BSREC) at the University of Warwick. All interviewed participants provided a written informed consent, and personal data collected from bite patients were anonymized upon case submission to the server maintained by the University of Warwick.

Clinic registry data, patient interviews and phone follow-up information as well as laboratory results were recorded using a tailor-made mobile phone-based application (BITERS – Bite Incidence Tool for Enhanced Rabies Surveillance; S3.3). The workflow of the data collection and information utilization is summarized in Figure 3.1.

3.2.4 Data analysis

We used the longitudinal data on patient and dog bite histories obtained through Integrated Bite Case Management to evaluate monthly throughput of patients across the three ABTCs, and to categorise the proportion of different stages of PEP completion and RIG administration. We then used the data to summarise the output of the study showing a successive breakdown of data from bite-victims to the completion of bite-history investigations.

To validate the potential use of the IBCM as an improved approach for dog rabies detection in the population, we tested for correlation between the number of dog cases classified as “rabies highly suspect dogs” and the number of laboratory confirmed rabies cases in each barangay by performing a generalized linear model with Poisson errors and a log link function. To further estimate the odds of finding a laboratory confirmed rabies case (i.e.

presence-absence) based on the number of “rabies highly suspect dogs”, we conducted a logistic regression model, using a logit link function. A positive relationship is to be expected in the case of a successful identification of cases tested as rabies positive. To assess the predictive power of the logistic model, we calculated the area under curve (AUC), with values above 0.5 and 0.7 indicating an acceptable and good model fit respectively.

To establish whether the reported bite incidence of patients presenting at the ABTCs corresponds to the number of rabies cases in the dog population, we conducted a linear Poisson regression model using first laboratory confirmed rabies cases an explanatory variable. To further explore other potential drivers of the reported bite incidence, we tested for a correlation between the patient bite incidence and vaccine shortage (linear regression with Poisson errors and an log link function), distance to ABTCs (linear regression with Gamma errors and an inverse link function), vaccination coverage, and distance to ABTCs and vaccination coverage and human population density (last two models as linear regression with Gaussian errors and an identity link).

Lastly, we employed the “rabies highly suspect” data identified to month and barangay to estimate their predictive power of future rabies occurrence. Specifically, we used logistic regression to model the probability that in a given month a barangay will receive at least one laboratory confirmed case based on the number of “rabies highly suspect” cases in the current and previous month, and from across four spatial scales including local (note, this variable was possible only for cases from a previous month), neighbouring barangays, municipality and province. Model selection was conducted using backwards elimination based on Akaike Information Criterion (AIC), with the final model being selected when no additional terms could be removed. Goodness of fit was evaluated by estimating the AUC.

Data on mass dog vaccination efforts were provided by Albay Provincial Veterinary Services (PVS) office and data on human population were taken from the Philippine Statistics Authority official website (Philippine Statistics Authority, 2016). We harnessed both data sources to reconstructed spatially refined maps of bite incidence per 1,000 per barangay and rabies presence, and to evaluate potential relationship between rabies burden across the province, dog vaccination coverage, and proximity to clinics.

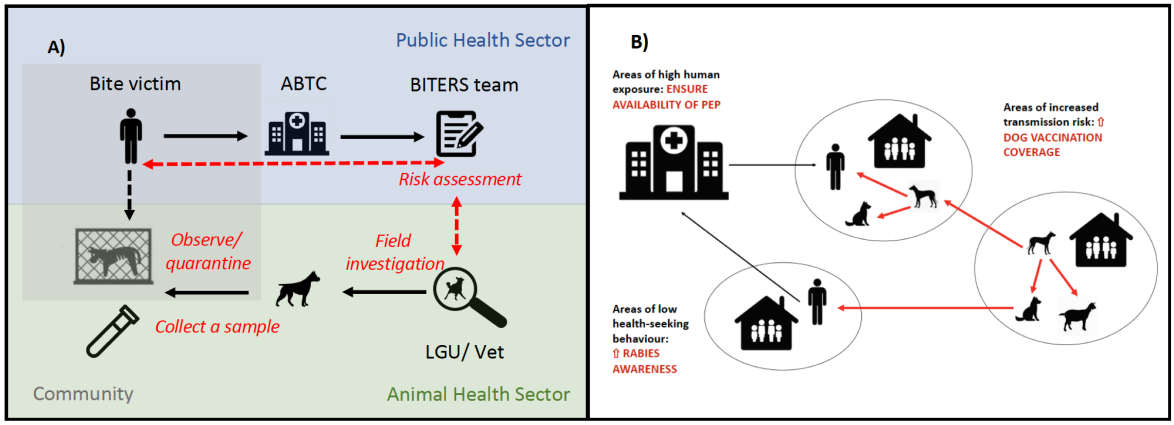

Figure 3.1: (A) Intersectoral case investigation. Blue shading indicates activities traditionally managed by the public health sector, green represents activities falling under the animal health sector and grey shading suggest measures that happen within the community. Black solid arrows refer to the action workflow, whereas red dashed arrows represent communication across sectors. A bite victim seeks treatment at an ABTC. Upon PEP administration, the patient's personal details are recorded, followed by an interview with a data collector who conducts risk assessment of the bite history background and health condition of the biting animal. If the case is considered to be high risk, a designated LGU/veterinary officer receives an alert to initiate a field investigation. All patients are advised to quarantine/observe the biting animal, and after a 14-day quarantine period contacted over the phone by the data collector to provide follow-up information on potential changes in the animal's health condition/behaviour. This information is further accessed and, if relevant, communicated to the LGU/veterinary personnel. Field investigations confirm animal status and where available, a brain sample is recovered and laboratory tested. **(B) Extraction and utilization of information through IBCM.** Black arrows indicate patient-driven actions, whereas events detectable through field investigations are represented by red arrows. Investigating incident histories of dog-injury patients, combined with tracing of rabid animals narrows down the source and spatial extent of infection. Data collected at ABTCs offer invaluable information on PEP demand and uptake, and a potential for more judicious clinic-based triage of patients requiring full course of PEP. Not all rabid dogs result in a human victim. Such cases, however, may still contribute to the overall transmission of the disease. Similarly, not all human victims seek healthcare. In both instances, surveillance quality can be increased through contact-tracing of transmission events preceding cases presenting at ABTCs, providing critical support in detecting rabies transmission pathways and identifying areas where dog vaccination and a victim's health-seeking behaviour require improvement.

To estimate monthly vaccination coverage in each barangay, we first projected monthly dog population sizes using the standard logistic growth model. We calculated the rate of population growth defined as $r = \frac{\log\left(\frac{N}{N_0}\right)}{T}$, where N and N_0 stand for final and initial population sizes respectively and T denotes the number of months between the two time points. We then utilised the growth rate r to project dog population sizes, N_t, at monthly timesteps t between March 2018 and March 2019 using dog count data recorded annually by the Albay PVS as part of mass dog vaccination campaigns. For barangays with missing dog counts we drew the local dog population size from a distribution of barangay-level population sizes within the home municipality.

In several places, the number of vaccines reported as used during the vaccination campaigns exceeded the actual dog population size. For barangays in which the reported number of dog vaccines resulted in more than 85% of dogs being vaccinated, we reallocated the vaccine doses proportionally to the overall number of dogs and vaccines available for the given month and barangay with the probability of getting vaccinated equal to $1 - (\frac{(N_t - 1)}{N_t})^{D_t}$ where D_t stands for the number of vaccine doses reposted as used in a given month t.

Vaccinations conducted more than six months after the last campaign were treated as annual dog vaccination campaigns. The achieved vaccination coverage V_t (at the timestep t) was assumed to wane exponentially, based on the average longevity of the vaccine w where $v = \frac{1}{w}$ (parameter values taken from Townsend et al., 2013) and the demographic turnover of the dog population bound by the birth rate b and death rate d (parameter values taken from Ferguson et al., 2015), yielding the following formula for coverage waning as $V_{t+\Delta t} = V_t e^{-(b+d+v)\Delta t}$. For barangays in which repeat vaccination occurred within six months of the previous campaign, we allocated vaccines to previously unvaccinated dogs remaining in the barangay population such as $V_{t+\Delta t} = V_t e^{-(b+d+v)\Delta t} + (1 - V_t e^{-(b+d+v)\Delta t}) \frac{D_t}{N_t}$.

3.3 Results

Utilizing data collected at the governmental ABTCs, we found that bite incidence in Albay is high (9073 bite-patients recorded between 1 March 2018 and 31 March 2019) with PEP administered mostly unsystematically. Due to a temporary vaccine shortage from April 2018 through to June 2018, 911 patients were referred to a private clinic where the vaccine is not provided free-of-charge, hence less prone to depletion. All patients treated at either of the ABTC facilities received at least 1 dose of PEP (8162 patients in total), 82% of patients received 2 doses and 73% patients received 3 doses. Only 17% of patients received the fourth dose, likely due to the cost patients are charged for the last dose. Additionally, 23% (1887 patients) received a dose of costly RIG (5400 PHP/106.5 USD for a dose of RIG per person). This is consistent with previous reports of generous use of PEP and RIG in the Philippines (Hampson et al., 2015; Rysava et al., 2019). We found that the total number of patients presenting at clinics varied significantly across months and showed no statistically significant relationship with the number of laboratory confirmed rabies cases (regression coefficient = 0.0009, p-value = 0.198, residual deviance = 27.25 on 11 degrees of freedom). Instead, the observed pattern likely reflects the vaccine shortage during the first quarter of the year as further statically supported (regression coefficient = -0.476, p-value < 0.005, residual deviance = 512.42 on 11 degrees of freedom) (Fig. 3.2a).

Ninety percent of patients presenting at the clinics reported dog bites as their primary injury, followed by 24% reports of dog scratches and <1% of open wound exposures to dog's saliva (N.B. several patients reported multiple injuries of different types). Three patients received a full course of PEP after being supposedly exposed to another rabies suspect person; however, no skin rupture occurred. Whilst most patients adhered to the WHO (World Health Organization) recommended bite management guidelines – washing their wounds thoroughly with water and soap for 15 minutes (indicating a wide-spread awareness on rabies prevention) – a large number of individuals also opted for the use of traditional medicine (i.e. tandok, tambal) and herbs.

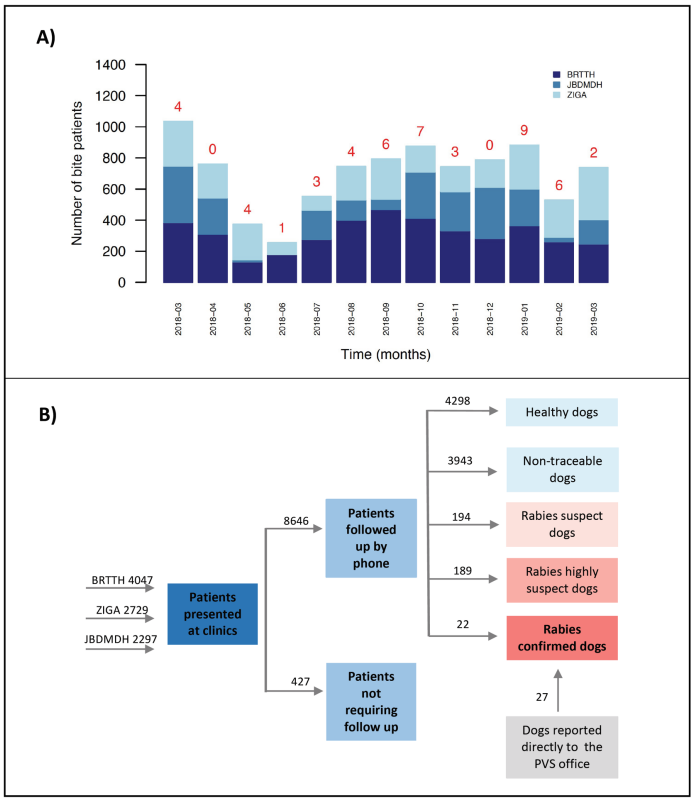

Figure 3.2: (A) Patient monthly throughput by clinic. Monthly distribution of patients presenting at the three ABTCs in Albay province between March 2018 and 2019. Red numbers above bars indicate rabies positive dog cases confirmed in each month. **(B) Investigation breakdown from recording of bite victims at the ABTCs to completion of investigation and case classification.** Numbers above arrows indicate the sum of cases in each category. Bite incidents recorded at the ABTCs were followed after a 14-day observation period to ascertain any behavioural or health related changes in the biting animal. Based on the protocol described in the Appendix (S3.1), investigated incidents were classified either as "Healthy", "Non-traceable", "Rabies suspect" or "Rabies Highly suspect". Only dogs that tested positive by FAT for rabies were classified as "Rabies confirmed". Note the acronym for Provincial Veterinary Services (PVS).

A majority of cases (6906) were provoked by the bite victim with 4298 animals found healthy after the 14-day observation period. Information collected during the initial interviews and phone follow-ups on the fourteenth day after the clinic attendance allowed us to differentiate between non-case incidents, incidents involving a potentially suspect dog and incidents for which the biting animal was untraceable after the initial encounter.

Specifically, we classified the incidents into one of five categories (Fig. 3.2b). For unvaccinated dogs either exposed to, or a puppy of, a rabid individual, symptomatic dogs, and dogs that died or were killed, a field investigation followed by brain sample collection was immediately prompted. Where sample collection was not possible, we classified the investigated dogs as "rabies highly suspect"; otherwise as either "rabies confirmed dogs" or "rabies laboratory negative". Individuals that disappeared before a field investigation could be initiated but showed aggressive behaviour/unprovoked biting were considered "rabies

suspect". Unimmunized dogs showing no or unclear symptoms at the time of the biting incident that could not be traced after the 14-day observation period were classified as "non-traceable".

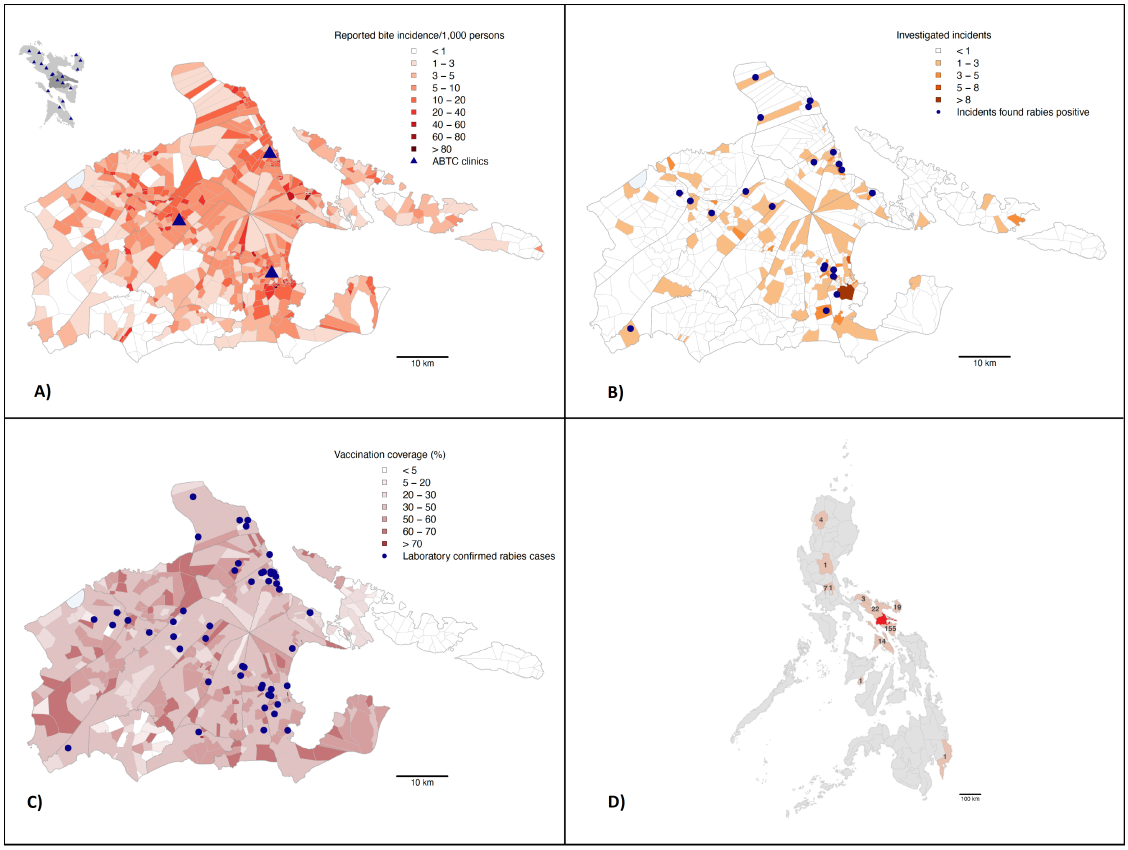

Figure 3.3: Summary maps of the BITERS surveillance data. Albay province shown in A (with Bicol region as an inset), B, and C. The Philippine archipelago shown in D. **(A)**. By barangay bite incidence reported at the three ABTC clinics in Albay province from March 2018 through to March 2019. The inset shows locations of ABTCs providing PEP to bite patients across the Bicol region (here as blue triangles) with Albay province indicated by a darker shade of grey. **(B)** Barangays shaded by the number of bite incidents identified for further field investigations through patient triage. Blue points show locations of cases classified as rabies positive, demonstrating the ability of the surveillance scheme to identify problematic areas. **(C)** The spatial distribution of laboratory confirmed dog rabies cases (blue points) in relation to dog vaccination coverage projected monthly at the barangay level and averaged across the study time period. **(D)** The number of bite patients who presented at an ABTC clinic in Albay whilst bitten outside the province. Source provinces of the identified incursions and Albay shown in lighter and darker red respectively.

All cases were initially considered for phone follow-up after 14 days of behavioural observation; however, in the instance of the bite incident being entirely provoked by the victim and the biting animal being vaccinated in the last 12 months (or exclusively kept indoors), the patient/animal owner was advised to observe the animal's behaviour and report back should any changes occur as opposed to being actively followed up on in 14 days. For all other cases, a strict quarantine was recommended, and for individuals classified as "rabies highly suspect" a relevant LGU officer was contacted to initiate a prompt field investigation.

An alarmingly low number of animals that caused the reported incidents were vaccinated (32% and 8% within the last 12 months and more than 12 months since the incident respectively) which was found to be approximately in line with the estimated vaccination coverage achieved during the mass dog vaccination campaigns (mean = 0.41, SD = 0.16 for each barangay across the study period). Further, both the vaccination coverage and patient bite incidence in each barangay correlated negatively with the distance to clinics (Fig. 3.3 and Figs. 3.4a, 3.4b). As such, barangays further away from the clinics were found to have been less likely visited for the mass dog vaccination campaigns during the study period. This pattern, however, also mirrors the spatial distribution of human population with densely populated barangays being clustered in and around urban areas where the ABTC clinics were situated, suggesting that the mass dog vaccination campaigns are predominantly targeted at barangays with high population densities (Fig. 3.4c). Whether the higher bite incidence occurring in barangays closer to the clinics implies that the health seeking behaviour is driven by increased rabies awareness (i.e. rabies awareness efforts more prevalent in urban settings) or rather discouraged by the distance required to travel in order to reach the clinics (or a combination of both) remains unclear. Interestingly, while the relationship between laboratory confirmed cases identified through the study and the distance to clinics follow the same trajectory, the distribution of these cases shows a wider spatial range ([0.9 – 36.8 km], mean = 8.05 km, SD = 7.08 km), suggesting a looser connection between urban centres and rabies transmission in dogs than we witnessed with regards to the human bite incidence.

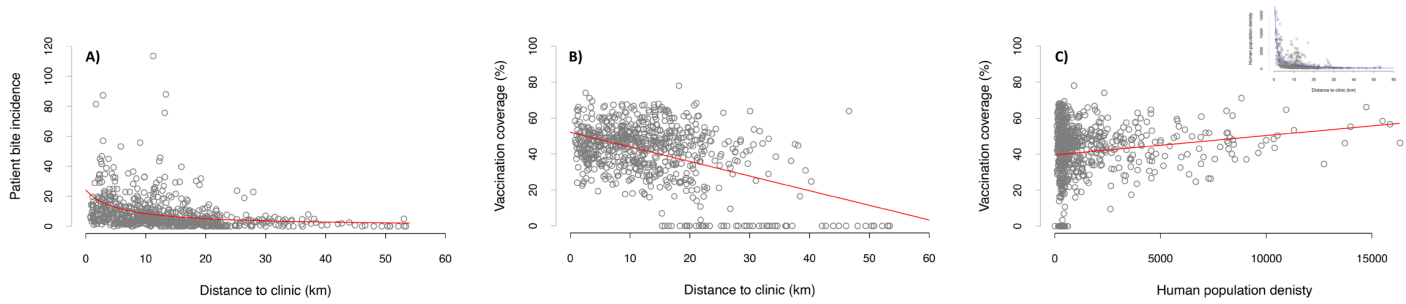

Figure 3.4: Summary regression analyses using BITERS surveillance data shown as grey points with lines indicating the fitted relationship based on the model output. (A) Relationship between barangay-level patient bite incidence and the Euclidean distance to the clinic from patients' home barangays (modelled as Gamma regression with inverse link, regression coefficient = 0.007 where the slope is defined as 1 / (intercept + regression coefficient * data, p-value < 0.005, residual deviance = 1213.3 on 718 degrees of freedom). **(B)** Relationship between barangay-level dog vaccination coverage (projected monthly and averaged across the time period of the study) and the Euclidean distance to the clinic from patients' home barangays (modelled as Linear regression, regression coefficient = -0.008, p-value < 0.005, residual deviance = 14.7 on 718 degrees of freedom); for truncated distance to 30 km (regression coefficient = -0.006, p-value < 0.005, residual deviance = 12.7 on 674 degrees of freedom.) **(C)** Relationship between barangay-level dog vaccination coverage (projected monthly and averaged across the time period of the study) and the barangay population density (modelled as Linear regression, regression coefficient = 1.075 e-05, p-value < 0.005, residual deviance = 18.6 on 718 degrees of freedom); inset showing the relationship between barangay-level population density and the Euclidean distance to the clinic from patients' home barangays, suggesting that the ABTC clinics are located in and surrounded by highly populated urban areas that tend to achieve higher vaccination coverage in the dog population (modelled as Gamma regression with inverse link, regression coefficient = 8.912 e-05 where the slope is defined as for the regression in Fig. 5a, p-value < 0.005, residual deviance = 549.82 on 717 degrees of freedom).

Based on the initial patient triage and phone call follow-up we originally identified 256 incidents (222 dogs as several patients were bitten by the same individual) classified as "rabies highly suspect" of which 6 patients were from the neighbouring province Sorsogon and one patient from Nueva Ecijia, a landlocked province in the Central Luzon region. For 33 of the rabies highly suspect dogs we conducted epidemiological field investigations; laboratory diagnostics confirmed rabies in 22 animals whilst 11 individuals tested negative.

In addition, 27 dog rabies cases were submitted to the Regional Animal Disease Diagnostic Laboratory by dog owners independently of the BITERS team field efforts. Submissions handled by dog owners could have been potentially encouraged by the increased rabies awareness through the presence of the field team in the area as all of the laboratory confirmed cases were found within the foci of investigations.

To examine the utility of the patient driven surveillance scheme and subsequently collected data for discerning dog exposures and detection of rabies in the dog population we tested the relationship between dog-exposure incidents classified as "rabies highly suspect" and laboratory confirmed rabies presence in each barangay across the province. We found that the number of monthly rabies highly suspect cases (at the barangay level) strongly correlated with both the probability of rabies occurrence and the number of laboratory confirmed rabies cases (Fig. 3.5a), providing a convincing evidence for the use of IBCM as an alternative and substantially more sensitive approach to rabies detection compared to the default routine surveillance of rabies in the Philippines. We further explored the spatiotemporal relationship between the probability of rabies occurrence in a given barangay and at a given month based on the number of rabies highly suspect cases across varying spatial and temporal scales (ranging from local barangay to the entire province, and in the current month and a month prior, given that the mean generation interval of rabies is ~25 days as in Hampson et al., 2009) (Figs. 3.5c, 3.5d). Through a series of progressively simplified binomial linear regression models (removing one variable at a time), we searched for variables (and combinations of variables) that provided the most predictive power to where positive cases could be expected given the data, and identified our final model based on the AIC value. The final model took a form of $log\frac{p_i}{1-P_i} = \beta 0 + \beta 1 LCprior_i + \beta 2 NCnow_i$, where $LCprior$ represent Highly Suspect cases in the focal barangay reported in the previous month, $NCnow$ represents Highly Suspect cases from neighbouring barangays reported in the current month, and the $\frac{p_i}{1-P_i}$ stands for the odds ratio of the observed value for a given observation event i. The results, therefore, suggest that rabies transmission happens mostly locally as cases tend to be clustered in space and time, with cases in the focal barangay from the previous month and current cases from neighbouring barangays having been most significantly predictive of future rabies occurrence (Fig. 3.5b).

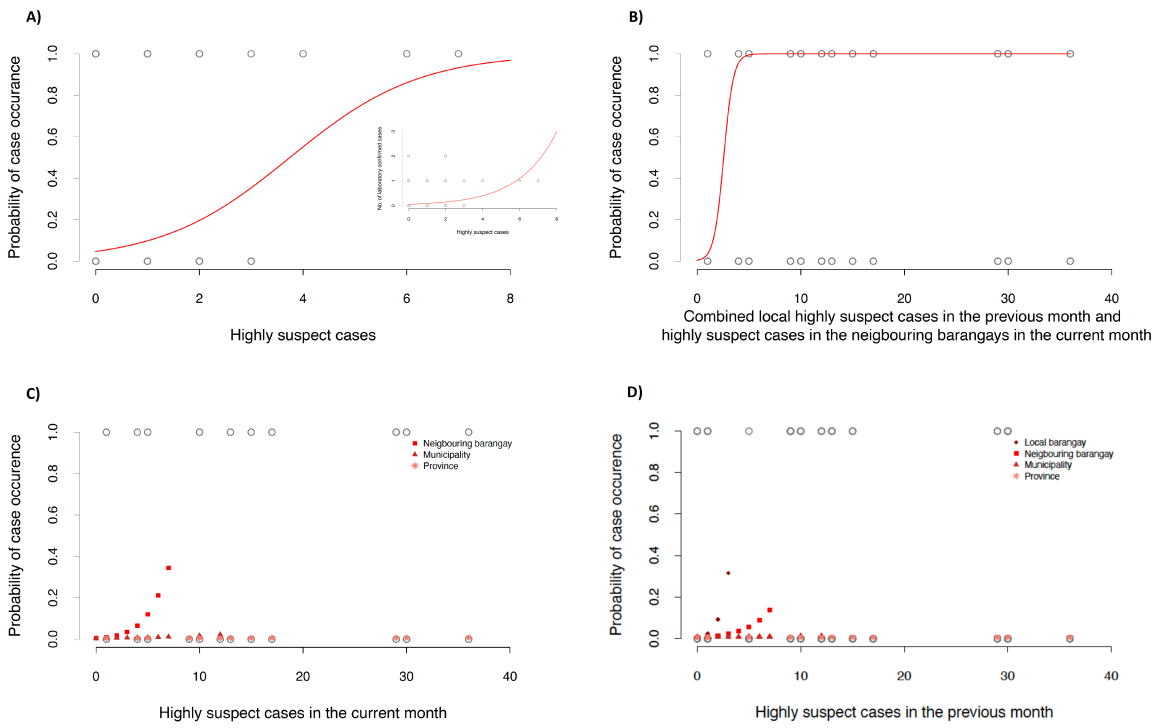

Figure 3.5: Validation and spatiotemporal analysis of the BITERS surveillance data. Top: (A) Relationship between the number of monthly rabies highly suspect cases in each barangay (x-axis) and the probability of detecting rabies (any number of laboratory confirmed cases) in the given month and barangay (y-axis) (modelled as Logistic regression, regression coefficient = 0.807, p-value < 0.005, residual deviance = 317.84 on 717 degrees of freedom, AUC=0.63). The strong positive association between the two variables suggests that the surveillance scheme may indeed offer a sensitive way to locate potential foci of infection both to obtain better estimates of rabies incidence in dogs (through such a targeted surveillance compared to routine surveillance) and to prevent further spread (through dog quarantine and increased rabies awareness). The inset depicts the same positive relationship between the number of monthly rabies highly suspects cases in each barangay along the x-axis and this time the number of laboratory confirmed rabies cases in the given month and barangay along the y-axis modelled as Poisson regression (regression coefficient = 0.501, p-value < 0.005, residual deviance = 252.77 on 717 degrees of freedom). **(B)** Probability of rabies detection based on the number of rabies highly suspect cases across spatial and temporal scales (modelled as Logistic regression). The final model fit (model selected using the AIC) shows that the probability of detecting rabies at barangay level increases sharply with the number of rabies highly suspect cases in the local barangay in the past month and rabies highly suspect cases occurring currently in neighbouring barangays (regression coefficients = 1.4757 and 0.657 for local highly suspect cases form the previous month and current highly suspect cases in neighbouring barangays respectively, p-value < 0.005 for both variables, residual deviance = 591.7 on 9344 degrees of

freedom, AUC=0.6). **Bottom:** The influence of the monthly rabies highly suspect cases on current **(C)** and future **(D)** rabies occurrence across different spatial scales ranging from local barangay to province level. Fitted relationship for all variables tested individually shown as points (x-axis) with spatial scales differentiated by colour and shape.

3.4 Discussion

In spite of various ongoing rabies prevention programmes, the Philippines currently ranks high in terms of bite incidence and human per capita rabies death rate both within Southeast Asia (OIE, 2016) and worldwide (Hampson et al., 2015). It is, therefore, apparent that there is a need to reduce the burden of rabies in the country, and to devise intervention policies that can minimise the risk to human health in the future.

ABTCs that provide post-exposure prophylaxis to humans have been established in every province across the Philippines, but the burden of incidence falls disproportionally on individual clinics depending on their accessibility, socioeconomic background of the region, and quality of surveillance. Often, with free provision of treatment and seemingly unlimited stocks, systematic risk-assessment of patients is lacking both by healthcare providers and patients themselves, leading to substantial precautionary use of PEP (Amparo et al., 2018a; Amparo et al., 2018b). In the Philippines, PEP use has been increasing in an unsustainable fashion. This inevitably resulted in PEP shortage across the country in the second quarter of 2018, and was further exacerbated by a wider global vaccine shortage (Amparo et al., 2018a; Rysava et al., 2019).

Here, we found that the patient bite incidence in Albay was high, with PEP administered universally, reflecting the availability of the vaccine and proximity to clinics rather than the actual distribution of rabies cases in the dog population. Fox example, all patients classified as Category I exposures based on the WHO classification of rabies exposures were administered at least one dose of PEP (with the majority completing a full course) despite such exposures not requiring vaccination according to the WHO guidelines (WHO, 2014). Similarly, costly RIG was often provided with substantial delays (as clinics usually store only small amounts or no RIG at all) at which point the medication had no actual impact as its purpose is to provide a fast protection before the vaccine-induced immunity response is

developed, and it should not be administered beyond day 7 after the initial dose of vaccine (WHO, 2018b). This appears an unnecessary expenditure, especially as the recent body of evidence suggests an outstanding effectiveness of PEP even in the absence of RIG (WHO Rabies Modelling Consortium, 2019). Considering >200,000 USD were spent on RIG over the course of the study, if RIG was reserved only to Category III patients with multiple exposures, vaccines for the entire dog population in Albay could have been procured utilizing the saved money (~2 USD on average per parental vaccination per dog USD [Miranda et al., 2017; Undurraga et al., 2020] and thus yielding a significantly more tangible impact on human health.

In response to the temporal PEP shortage, many patients were redirected to acquire vaccines from private clinics at their own cost, precipitating additional inequity in access to healthcare as the relatively high cost of the vaccine may be largely prohibitive to communities of lower socioeconomic status (Amparo et al., 2018b). Our results are directly in line with similar reports from other provinces across the Philippines, highlighting the urgency for discerning PEP administration to identify true high-risk patients, and to prevent unnecessary causalities caused by depleted vaccine stocks (Amparo et al., 2018a; Rysava et al., 2019). Whilst it is an ethical imperative to improve access to PEP for those at risk, indiscriminate PEP administration associated with excessive expenditure on non-case patients results in financial strains and vaccine shortages. Moreover, an ongoing chance of human deaths persists for as long as rabies continues to circulate in domestic dog populations. This particularly jeopardizes marginalized and hard-to-reach communities that tend to be adherent to traditional customs (including low health-seeking behaviour) and are only ever detected by the passive surveillance system (Hampson et al. 2016; Rajeev et al., 2019).

Both human deaths due to rabies and rabies cases in dogs are severely underreported as a result of underfunded and/or outdated surveillance systems (Hampson et el., 2016). Proper assessment of the extent of transmission is, however, needed, for a multitude of reasons. A false impression that rabies might not be as widespread as it in reality is can lead to low prioritization of control and management programmes, especially in settings where rabies competes with other diseases of “higher” economic importance. Resource allocation for

rabies control may then be suboptimal, short-lived or spatially inconsistent which is particularity detrimental to the success of mass dog vaccination campaigns. Furthermore, regardless of the epidemiological status an area may be experiencing (e.g. epidemic, endemic, etc.), it is unlikely to be able to credibly evaluate the effectiveness of implemented interventions and the progress made towards elimination of the disease without appropriate surveillance and monitoring.

The surveillance protocol piloted in this study facilitated a threefold increase in the detection of laboratory confirmed rabies cases in dogs, from 12 cases in the previous 13 months to 49 cases during the study period. There is no conclusive evidence that the increase in reported cases would be a result of waning vaccination coverage. The heterogeneity of the coverage may, however, play a role in providing opportunistic pockets of susceptibility as the reported cases were mostly localized. Rabies circulates at a very low prevalence (with death rates estimated to be less than 1% of the dog population per annum [Hampson et al., 2016]), and even during epidemic phases depletion of susceptible dogs has never been observed. This is, however, only true at the population level, and the transmission dynamics are likely to be substantially more sensitive to system changes at finer scales. Nonetheless, the vaccination coverage in Albay falls consistently far below the recommended 70%. Thus, while the barangay-level differences in the number of immunized dogs may have exacerbated the intensity of the reported outbreaks, they did not cause them.

The spatial pattern of the reported cases is more likely to be related to the very nature of rabies transmission. Individual dogs travel on average 0.88 km (per single movement trajectory) and tend to be territorial with regards to their owners' households (Hampson et al., 2009). Our spatiotemporal statistical analysis suggests that the transmission of rabies between dogs takes place in clusters, with the highest probability of receiving a case in a barangay being within two months from a case being reported focally or in a neighbouring barangay. Such results are somehow intuitive, particularly given the length of the rabies serial interval, but they have potentially pivotal management implications. Barangays that at the time experience rabies cases, as well as their neighbours, should be on guard for future transmission and taking measures such as adhering to enhanced surveillance, practicing

risk-adverse behaviours, and quarantining all rabies suspect dogs. Where vaccination coverage is low and vaccines are available, reactive vaccination may provide some benefits, but is not be sufficient without annual comprehensive mass vaccination campaigns (Purwo Suseno and Rysava et al., 2019).

Exogenous incursions represent an additional risk of infection, given the highly connected landscape that exists in the Philippines. The number of viral strains circulating within the region and their origin can be assessed only by viral whole genome sequencing. Including genomic surveillance in the IBCM scheme is yet to be made routinely available, but it is fully feasible and has been already piloted in the Philippines using the samples collected through this study in Brunker at al. (2020).

Integrated One Health approaches of rabies surveillance have the potential to substantially increase case detection, and inform more judicious and cost-effective ways for PEP provisioning, while proactively identifying areas and individuals most at risk who would otherwise not receive attention or seek care. Similar IBCM/enhanced surveillance studies have been trialled around the world (Etheart et al., 2017; Lechenne et al., 2017; Rajeev et al., 2019; Luhasi at al., 2020, Ma et al., 2020). Whilst the underling structure of such integrated surveillance schemes remain the same, their operational aspects are context specific. Surveillance data are often pitched as useful for parametrization of complex models, for estimating disease burden, understanding health seeking behaviours, and as an early warning to prevent future outbreaks. Combining all of the requirements within a single-source dataset may, however, be unrealistic, and potentially misleading (i.e. as different type of information entails a tailored approach to data collection), while at the same time surveillance databases overflow with worthless information. Experimental design for health data needs to take on account local dynamics, both political and ecological, and be built with a clear idea about the specific kind of data/information that will be feasible to collect and useful in the local settings. While the broader concept of such studies may not be unique, the type of operational research done with respect to the needs, expectations and customs of local communities certainly is.

Leveraging the One Health ethos to build and strengthen intersectoral collaboration (including collaborative investments between public health and veterinary services) is of the

utmost importance as even with universal health programmes, uptake of vaccines is not uniform. The risk of exposure is disproportional depending on the geographic location and the socioeconomic background of an individual, and the physical access and cost of attending a clinic remains differential.

CHAPTER 4

Supplementary measures towards rabies elimination – exploring dynamical changes of rabies transmission under quarantine

4.1 Introduction

Mathematical and statistical modelling has been widely applied in the field of quantitative epidemiology since the first half of the twentieth century; its history within the field dates back to 1927 when Kermack and McKendrick (1927) first introduced the concept of disease transmission governed by a set of ordinary differential equations. Different approaches can be taken to model disease transmission, ranging from statistical forecast type models to complex computational simulations. All models are to some extent used to shed light on disease dynamics; however, while some are more tailored towards understanding the evolutionary and ecological pathways of disease systems, others can be used to guide policy decisions in designing and/or refining intervention strategies via model predictions. The diversity of modelling approaches is of a great advantage to the field as each model type can play a distinct role in the process of knowledge acquisition.

Practical problems, however, arise when employing modelling in epidemiology as formulating and parametrizing a model is no simple task. Disease systems are complex in that they typically involve multiple drivers demonstrating different patterns of interaction across multiple scales, of which many remain poorly understood and are difficult to support with data as quantifiable empirical evidence may not always be available. Increasing model complexity potentially improves its accuracy by including more biological realism, but it compromises the model's feasibility given extensive information demands (Keeling and Rohani, 2008). Data of variable quality and magnitude, and substantial heterogeneity in key epidemiological and ecological parameters of a disease and its host and/or vector populations leads to uncertainty that hinders both the model's potential to capture the dynamics of the disease and its decision-making power. This creates an obvious conundrum and ultimately trade-off between practicality and realism of a model. While accuracy is always a limited article and simplified assumptions are inevitable, modelling provides a

tractable approach to conceptualization of a system in a successive and tangible way (Grassly and Fraser, 2008).

Canine rabies, an acute zoonotic infection, has been long an enigma in the field of quantitative epidemiology. While deceivingly easy to trace (and hence parametrize) as transmission happens predominantly among domestic dogs through saliva of an infected individual, model-based predictions are scarcely ever consistent with empirical observations (Rajeev et al., 2020). It is likely due to the complexity and many interdependent factors of the system that the traditional epidemiological models fail to translate to the real-world dynamics in their entirety. The details of how rabies transmission operates across spatial, temporal and population scales remain unclear; however, broader aspects of the disease epidemiology have been widely explored. International organizations have committed to the global elimination of human deaths from dog-mediated rabies by 2030, and scientific guidance to facilitate progress towards elimination has been underway (Minghui et al., 2018; WHO, 2018).

Decades of operational experience supported by a mounting body of modelling work conclusively demonstrate that mass vaccination of the dog population is the single most important and cost-effective way to control rabies (Coleman and Dye, 1996; Townsend et al., 2013; Ferguson et al., 2015). While implementation of high coverage-achieving, spatially comprehensive annual mass dog vaccination campaigns should be prioritized where possible, the desired control efforts may be impeded by logistical constraints such as availability of resources and limited manpower. Supplementary measures to support vaccination campaigns where coverage (temporarily) falls below the recommended threshold (<70% in WHO, 2013) are, however, sparse, and often focused on culling of dogs that has been repeatedly shown ineffective in the case of rabies (Morters et al., 2012; Townsend et al., 2013; Purwo Suseno and Rysava et al., 2019).

While immunization of the susceptible population is the primary intervention strategy in the modern world, quarantine – understood as an isolation of confirmed or suspect infectious cases – is one of the oldest, low-technology forms of disease control (Keeling and Rohani, 2008). Transmission potential of an infectious disease is driven by the basic reproduction

number ($R0$), defined as the average number of secondary cases caused by an infectious individual in a naïve (unimmunized) population. $R0$ depends on the probability of infection given contact between an infectious and susceptible individual, the length of infectious period, and the number of contacts an infectious individual has per a unit time (Bjørnstad, 2018). Both intervention strategies operate by lowering $R0$ through reducing the number of disease-exposure contacts among hosts. Vaccination focuses on the reduction of susceptible individuals available to infection, and is particularly effective for highly transmissible diseases where a large proportion of a population would be exposed to the disease agent (Bansal et al., 2006; Glasser et al., 2016; Lee and Chowell, 2017). For infections that circulate endemically at low prevalence, or infections at the early stages of an outbreak, contact-tracing followed by quarantine of suspect/infectious individuals provides a highly sensitive tool to curtailing the transmission potential of a disease (Klinkenberg et al., 2006; Pandey et al., 2015; Berge et al., 2018).

Here we sought to develop an epidemiological model for rabies transmission to examine the effects of quarantine on the disease dynamics. We first focused on the development of a structurally simple analytical model to explore the qualitative impact of quarantine on the long-term behaviour of the system, specifically interested in analysing the theoretical underpinnings of disease persistence and extinction for low transmissibility diseases. Building upon the conceptual understanding gained though the mathematical models, we then expanded the existing baseline framework by incorporating probabilistic features relevant to rabies ecology. This allowed us to quantitatively investigate the changes in rabies dynamics under the following scenarios: (1) no quarantine, (2) quarantine of dogs identified through bite-histories of patients presenting at clinics, and (3) enhanced quarantine informed by contact-tracing of rabies suspect and highly suspect dogs identified through bite-histories of patients presenting at Animal Bite Treatment Centers (ABTCs).

4.2 Methods

4.2.1 Analytical world: The theory of rabies

A base modelling framework commonly used to understand disease dynamics in a population, referred to as a “compartmental model”, is a mathematical model governed by a system of equations formulated to recapitulate the mechanisms of disease transmission.

Modelled populations in such models are divided into individual “compartments” representing successive stages of an infection; individuals from one compartment transition into another at a given rate, commonly known as a model “parameter”. Behaviour of each compartment is understood as a function of time evolving according to a preconceived mechanistic relationship.

Compartmental models are conceptual and qualitative in the sense that they are not attempting to make predictions about a particular number (e.g. the exact number of new infections), but they are rather used to understand the types of longer-term, global dynamics that might occur. Usually deterministic (investigated through a system of ordinary differential equations), they, however, can be extended to further realism (in a stochastic “random” framework) and built at different complexities (e.g. multi-compartmental models, age-structured models, metapopulation models, etc.).

The simplest, canonical formula underlying the vast majority of mathematical epidemiological models is called an S-I-R (Susceptible – Infected – Recovered) model, governed by the system of Ordinary Differential Equations (ODEs) shown below.

$$\frac{dS}{dt} = \mu N - \beta I \frac{S}{N} - \mu S \tag{1}$$

$$\frac{dI}{dt} = \beta I \frac{S}{N} - (\mu + \gamma) I \tag{2}$$

$$\frac{dR}{dt} = \gamma I - \mu R \tag{3}$$

Here, susceptible individuals becomes infected upon contact with an infected individual at the rate β (transmission rate; $R0(\gamma + \mu)$; (note that $\frac{S}{N}$ here denotes the susceptible fraction of the population which infected individuals will encounter, assuming infected individuals mix freely and can come in contact with any compartment within the system), infectious individuals recover from the infection at the rate γ (recovery rate; $1/infectious\ period$), and all individuals leave the population as a result of a natural death

at the rate μ. New susceptible individuals are born at a per capita birth rate μ where $N = S + I + R$, and the population size is assumed to be constant (i.e. $\frac{dN}{dt} = 0$).

When one of the compartments (S, I or R) reaches its maximum or minimum value, its rate of change equals zero. Only when all rates of change are equal to zero, the dynamics of the system are at an "equilibrium" or so called "fixed points"; here $\frac{dS}{dt} = \frac{dI}{dt} = \frac{dR}{dt} = 0$. This disease system has two equilibria: a disease-free equilibrium E_0 in which quite intuitively $S_0 = 1$, $I_0 = 0$, and $R_0 = 0$, and an endemic equilibrium $E^*$where $S^* = \frac{\mu+\gamma}{\beta}N$, $I^* = (\frac{\mu}{(\mu+\gamma)} - \frac{\mu}{\beta})N$, and $R^* = N - I^* - S^*$ for the Equations (1), (2), and (3).

However, whether a system is likely to be observed at its fixed points depends on the stability properties of the fixed points to small perturbations. In mathematical terms, fixed points of a system are locally stable only if all real parts of eigenvalues (λ) of the system's Jacobian matrix (J), when evaluated at the equilibrium, are less than zero. To find eigenvalues, we need to solve the determinant of the Jacobian set as $\det(J - \lambda I_n) = 0$, where I_n represents the "identity matrix". Assuming that $f = \frac{dS}{dt}$, $g = \frac{dI}{dt}$, and $h = \frac{dR}{dt}$ where *f*, *g* and *h* are functions of *S*, *I* and *R*, the Jacobian of the SIR system is given by

$$J = \begin{pmatrix} \frac{\partial f}{\partial S} & \frac{\partial f}{\partial I} & \frac{\partial f}{\partial R} \\ \frac{\partial g}{\partial S} & \frac{\partial g}{\partial I} & \frac{\partial g}{\partial R} \\ \frac{\partial h}{\partial S} & \frac{\partial h}{\partial I} & \frac{\partial h}{\partial R} \end{pmatrix}$$

.

Applying this principle to the Equations (1), (2), and (3) we get

$$J = \begin{pmatrix} -\frac{\beta I}{N} - \mu & -\frac{\beta S}{N} & 0 \\ \frac{\beta I}{N} & \frac{\beta S}{N} - \mu - \gamma & 0 \\ 0 & \gamma & -\mu \end{pmatrix}$$

.

Now we subtract λ from the diagonal elements and calculate the determinant. This gives us the following characteristic polynomial equation

$$\left(-\frac{\beta I}{N}-\mu-\lambda\right)\left(\frac{\beta S}{N}-\mu-\gamma-\lambda\right)(\mu-\lambda)+\left(\frac{\beta I}{N}\right)\left(\frac{\beta S}{N}\right)(-\mu-\lambda)=0 \tag{4}$$

where $(-\mu-\lambda)$ can be immediately factored out, giving us our first eigenvalue for both the disease-free and endemic equilibrium $\lambda_1=-\mu$. To find the remaining four eigenvalues (two for both E_0 and E^*; note that for a system of n ODEs the will be n eigenvalues), we will need to substitute the S and I terms with their solutions when at fixed points into the following equation

$$\left(-\frac{\beta I}{N}-\mu-\lambda\right)\left(\frac{\beta S}{N}-\mu-\gamma-\lambda\right)+\left(\frac{\beta^2 SI}{N}\right)=0\,. \tag{5}$$

In the case of the disease-free equilibrium where $S_0=1$ and $I_0=0$, the searched for solutions are $\lambda_2=-\mu$ and $\lambda_3=\beta-(\mu+\gamma)$. To ensure stability of this equilibrium (all eigenvalues must be strictly negative) β has to be smaller than $\mu+\gamma$; in other terms $R0<1$. This is largely intuitive, as if the birth and recovery rates transcend the transmission rate, meaning the secondary number of infected cases stays below 1, despite potential perturbations, the modelled dynamics will not result in an epidemic.

For the endemic equilibrium, we first express $S^*$and I^* in terms of $R0$, such as $S^*=\frac{\mu+\gamma}{\beta}N=\frac{1}{R0}N$ and $I^*=\left(\frac{\mu}{(\mu+\gamma)}-\frac{\mu}{\beta}\right)N=\frac{\mu N}{\beta}(R0-1)$ into Equation (5) which will give us the following quadratic equation

$$\lambda^2+\mu+\frac{\beta\mu N(R0-1)}{R0}=0 \tag{6}$$

By solving the quadratic using the standard formula, we finally obtain the last two eigenvalues for the endemic equilibrium

$$\lambda_{2,3}=\frac{-\mu R0}{2}\pm\frac{\sqrt{(\mu R0)^2-4(\mu+\gamma)\mu N(R0-1)}}{2} \tag{7}$$

Now, for $\lambda_{2,3}$ to take on negative values – in order for the endemic equilibrium to be stable – $4(\mu + \gamma)\mu N(R0 - 1) > 0$, and thereby $R0 > 1$ for the epidemic to persist.

For fixed points that are strictly stable or strictly unstable, an equilibrium is either a node or a focus depending on the structure of the largest eigenvalue – a distinction which governs trajectories in proximity to the equilibrium points. Specifically, for eigenvalues that have only a real part (a) the state trajectories move monotonically towards or away from the node equilibrium. On the other hand, for eigenvalues composed of conjugate pairs of complex numbers ($a + bi$) the state trajectories spiral towards or away from the focus equilibrium. The frequency at which the state trajectories spiral or oscillate towards fixed points is often referred to as resonant periods of stable foci and are determined by the imaginary part of the complex number (b) multiplied by 2π. Such periods change with transmission rate and infectious period of a disease and are expected to evolve towards slower convergence as $R0$ comes closer to 1. Therefore, less frequent outbreaks of a lower amplitude can be positively modulated by intervention strategies (operating through reducing the value of $R0$), while the ability to predict recurrent outbreaks and their average periods allow for context-specific surveillance and prevention programmes.

To explore the impact of intervention strategies that might be applied to the system, we first expanded the original SIR model by two additional compartments representing "vaccinated" and "quarantined" individuals in the population. The updated SIRVQ model is govern by the following equations

$$\frac{dS}{dt} = \mu N - \beta I \frac{S}{N} - \mu S - vcS + wnV \tag{8}$$

$$\frac{dI}{dt} = \beta I \frac{S}{N} - (\mu + \gamma + q)I \tag{9}$$

$$\frac{dR}{dt} = \gamma I + \tau Q - \mu R \tag{10}$$

$$\frac{dV}{dt} = vcS - (\mu + wn)V \tag{11}$$

$$\frac{dQ}{dt} = qI - (\mu + \tau)Q \tag{12}$$

where the total population $N = S + I + R + V + Q$, and V and Q represent the "vaccinated" and "quarantined" compartments respectively. Vaccination of susceptible individuals occurs at the rate vc, whereas the following loss of immunity takes place at the rate wn given by $1/the\ avergae\ longevity\ of\ the\ vaccine$. This model is not representative of rabies as infected individuals return to the population with complete immunity to future exposures, a transition required to maintain a closed population (i.e. $\frac{dN}{dt} = 0$). However, the above framework provides an initial step for evaluation of intervention strategies with regards to the longer-term dynamics of a system with low transmission potential such as rabies.

The following SISVQ formulation offers a way to approximate the lack of immunity upon rabies exposure while maintaining the population constant.

$$\frac{dS}{dt} = \mu N - \beta I \frac{S}{N} - \mu S - vcS + wnV + \gamma I + \tau Q \tag{13}$$

$$\frac{dI}{dt} = \beta I \frac{S}{N} - (\mu + \gamma + q)I \tag{14}$$

$$\frac{dV}{dt} = vcS - (\mu + wn)V \tag{15}$$

$$\frac{dQ}{dt} = qI - (\mu + \tau)Q \tag{16}$$

Here the total population $N = S + I + V + Q$ with infected individuals both in and outside of quarantine ($I\ and\ Q$) returning to the population as susceptible "puppies". In reality, rabies causes an unavoidable death to exposed dogs, in addition to births and deaths rarely ever happening at the same rate. For the purposes of the stability analysis, we can, however, assume that birth rates are altered as a result of dog losses due to the infection. This phenomenon has been repeatedly observed in field – dog owners regularly replace

their deceased dogs with new puppies that would not be sought out otherwise (and either be killed shortly after birth or abandoned to starve to death).

For both of the two intervention ODEs systems we assign $f = \frac{dS}{dt}$, $g = \frac{dI}{dt}$, $h = \frac{dV}{dt}$, and $j = \frac{dQ}{dt}$. Following the same methodology as described for the simple SIR model with no intervention compartments, we found fixed points of the SIRVQ and the SISVQ models in their endemic states, and explored the respective stability properties across a range of varying transmission (through altering the value of $R0$), quarantine (q) and vaccination (vc) rates. A flow diagram for both models is shown in Figure 4.1.

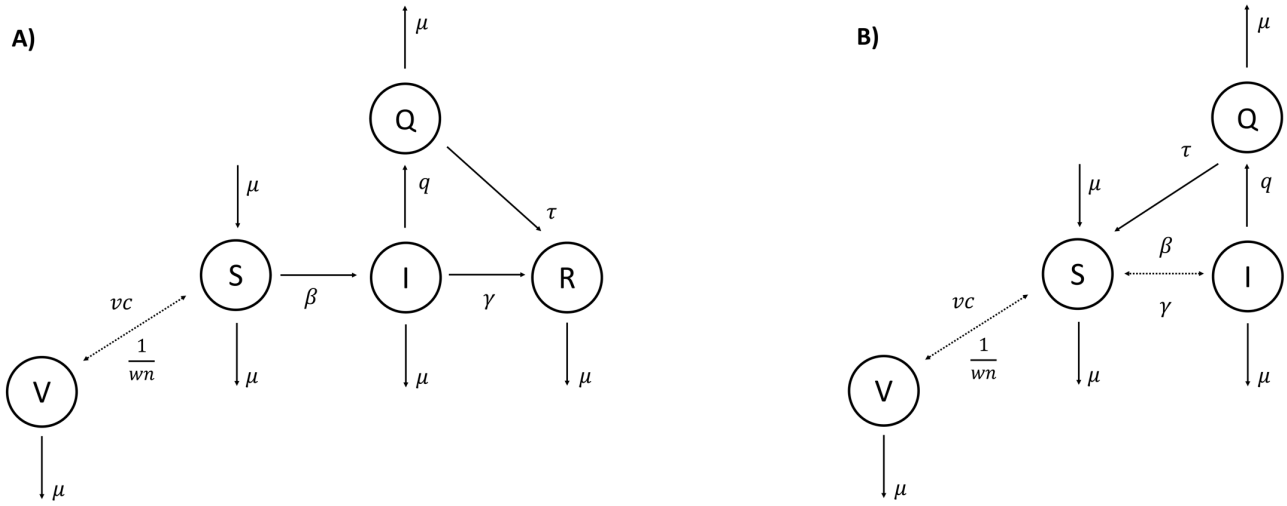

Figure 4.1: Single-species deterministic compartmental model diagram. Epidemiological classes are indicated by circles (where "V" and "Q" represent Vaccinated and Quarantined fraction of the population respectively), and arrows suggest the directionality of transitional flows of individuals and the virus moving between compartment. Susceptible individuals can become either Infected at the rate β as in the case of the SIR model, or Vaccinated at the rate vc. Vaccinated individuals then return to the Susceptible class with waning immunity of the vaccine at the rate given by $1/the\ avergae\ longevity\ of\ the\ vaccine$. Unlike in the case of the SIR model, here Infected individuals can be taken out of their class and placed into Quarantine at the rate q. (Please note that here we assumed that only Infected individuals can transition into the Quarantined class.) **(A) SIRVQ:** In this scheme, all infectious dogs leave the population and become Recovered at the rate γ for Infected individuals and the rate τ for the Quarantined dogs where $\frac{1}{\tau} = \frac{1}{\gamma} - \frac{1}{q}$ and $\tau = \frac{\gamma q}{q-\gamma}$, assuming all Quarantined individuals will always terminate in the Recovered compartment. **(B) SISVQ:** Here all infectious individuals (Infected and Quarantined dogs) leave the population at the same respective

rates as in the case of the SIRVQ model, but instead of terminating in the Recovered compartment, such individuals are returned to the population as Susceptible "puppies".

4.2.2 Computational world: The chance of rabies

In order to introduce a degree of biological realism, we expanded the existing SIRVQ model by the following additions that we believed were most relevant from the empirical work (Fig. 4.2). We first (1) introduced the role of stochasticity by modelling both the disease and population dynamics as a probabilistic process, (2) re-defined the transmission rate to capture heterogeneity in individual biting behaviour, and (3) allowed for exogenous incursions to enter the population. Given most dogs contracting rabies will become infectious within one month since the exposure, we also (4) included an "Exposed" compartment to account for the effect of incubation period on the dynamics of the disease. We then redefined the R compartment to represent all dogs "Removed" from the population by natural death and the disease (5). Lastly, we extended the single host model to (6) include transmission from dogs to humans, and (7) to incorporate information on health-seeking behaviour and post-exposure prophylaxis (PEP) uptake collected through a longitudinal enhanced surveillance study of dog bite-injury patients (described in detail in Chapter 3) in order to approximate the probability of quarantine.

Specifically, we modelled the time stepping process weekly using the Tau leap algorithm. We then parametrized rabies transmission explicitly as the number of rabid bites per infectious individual. Offspring cases (here representing a secondary case resulting from a biting incident caused by a primary case individual, not a vertical transmission from a parent to its offspring) were drawn from a negative binomial distribution as

$$\beta i \sim NegBinom\ (R0, k)$$

where $R0$ and k take different values for humans and dogs. The total transmission rate β at each time step was then formulated as a sum of all offspring cases present in the system at the modelled time step, and distributed proportionally to the size of each compartment available to exposure (all except for individuals in Quarantine).

$$\beta = \sum_{i=1}^{\mathrm{I}} \beta i$$

Incursions ic were drawn from a Poisson distribution where

$$ic \sim Poiss(\bar{\imath})\ .$$

The true rate at which a location receives an incursion will likely vary over time as control is implemented in neighbouring provinces, and geographically given the localized heterogeneous nature of rabies incidence. Here, we incorporated incursions to maintain fluidity in the disease system but set the value to function only as a "background" rate ($i = 1.5$).

We defined dog quarantine as the number of dogs identified through a triage of patients presenting at clinics. The number of quarantined dogs was then drawn from a Conway-Maxwell-Poisson distribution

$$Qi \sim CMPoiss\ (q, range)$$

where q and $range$ differ between investigations of case and non-case incidents. For rabies exposed and infectious dogs (divided proportionally according to the duration of incubation and infectious periods) identified through patient investigations, the total number of dogs per time step moved into quarantine was then calculated as

$$\sum_{i=1}^{\mathrm{Vh}} Qi * \eta$$

with η probability that the dogs identified through following rabid animals responsible for exposed case patients are also infected with rabies (i.e. exposed or infectious). From field observations we believe that η is relatively high, but for modelling purposes here we opted for a more conservative assumption of 70% as more data are needed for rigorous estimates.

Otherwise, the dogs responsible for non-case incidents both in humans and dogs were distributed proportionally to the size of each relevant compartment (i.e. S, E, Q, and V within the dog population).

Given the duration of incubation period is longer than the duration of quarantine (22.3 [Hampson et al. 2009] and 14 days respectively), a fraction of rabies exposed quarantined dogs may not become symptomatic before their release. To account for such a possibility, we explicitly generated days until symptomatic for each exposed dog held in quarantine, and returned those individuals showing no symptoms after the 14-day period back into the population.

Immunity of humans vs was defined as achieved through administration of PEP upon attendance at a clinic (note, here we assumed that two doses of PEP delivered at days 1 and 7 would provide immunity). The weekly proportion of bite-injury patients (ε) was drawn from a zero truncated normal distribution of weekly throughput records collected at the ABTC clinics, described in Chapter 3. The percentage of rabies exposed humans that will receive PEP (μ) varies extensively across geographical areas and socioeconomic backgrounds. Here, we assumed that with enhanced surveillance 80% of human cases would be detected in a timely manner and administered the lifesaving vaccine.

The rate of dog vaccination vc was estimated using vaccination records provided by Albay Provincial Veterinary Services office. We first calculated by barangay monthly vaccination coverage for the entire province from 2018 through to 2019, using methods described in Chapter 3. For each week we then drew the vaccination rate from a zero inflated beta distribution of monthly vaccination coverages averaged across the province. Lastly, we incorporated bias in re-vaccination of dogs (vv) directed towards individuals that are easy to capture for administration of the vaccine. All parameters are summarized in Table 4.1.

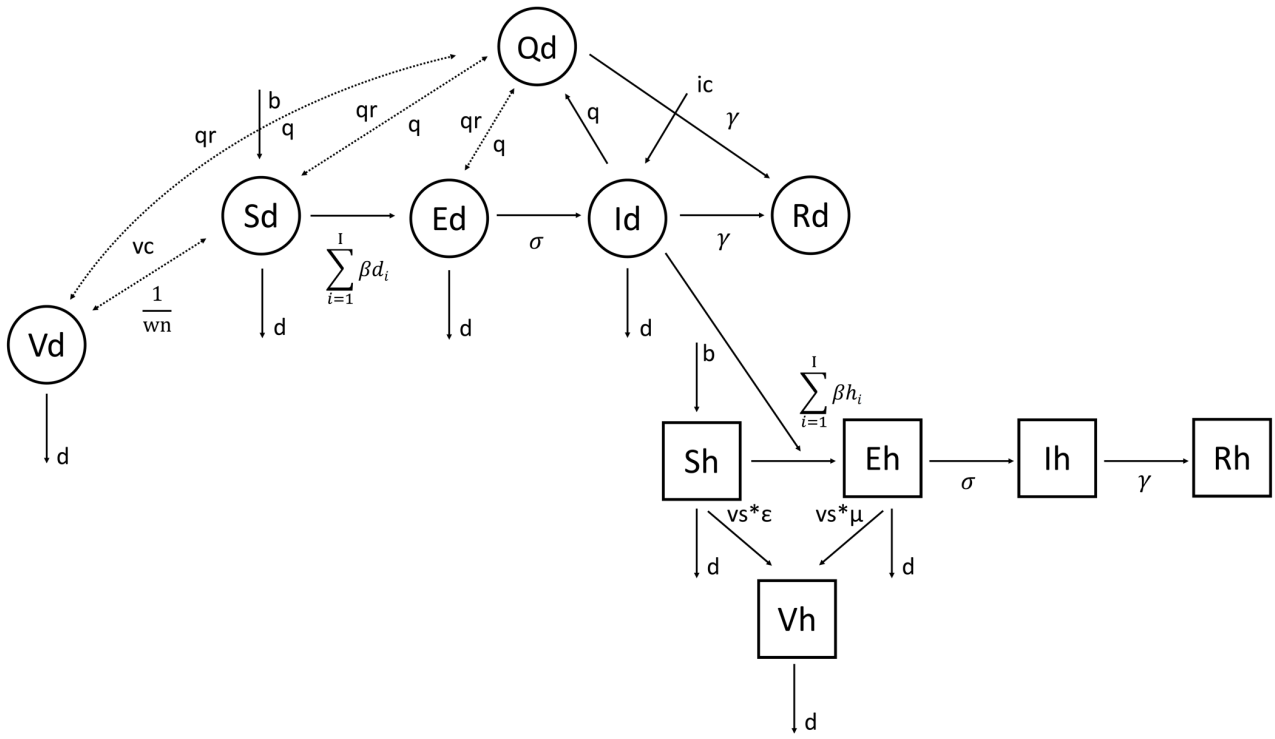

Figure 4.2: Multi-species SEIRVQ compartmental model diagram. Dog and human epidemiological classes are indicated by circles and squares respectively. Arrows show directions at which individuals and the pathogen move through the system. Here we expanded the representation of the progression of the disease by adding an Exposed compartment, capturing individuals who have contracted rabies but will become Infectious with a time lag associated with incubation period defined as $\frac{1}{\sigma}$. We also allowed for any epidemiological class of the dog population (except for the Recovered/Removed class) to be placed in quarantine. Susceptible and Vaccinated quarantined dogs are returned to their respective compartments upon completion of the quarantine at the rate qr. Infected quarantined dogs are removed from the population as a result of disease-induced death at the rate γ. Depending on the progression of the disease in Exposed quarantined dogs, two distinct scenarios can occur. For those individuals that will become symptomatic/Infected within the timeframe of their quarantine, disease-induced death follows at the same rate as for Infected individuals, whereas Exposed quarantined dogs asymptomatic by the end of their quarantine are returned back into the Exposed class at the rate qr. Transmission of the disease between dogs, and from dogs to humans is defined as a sum of offspring rabid bites seeded by Infected individuals, drawn from a negative binomial distribution taking different parameter values for dogs and human. Lastly, the overall level of infection in the system can be increased by an introduction of exogenous incursion entering the system at the rate ic. All model parameters associated with the disease and demographic process illustrated here are summarized in Table 4.1.

Table 4.1: Summary of SEIRVQ model parameters. Parameter values are provided for dogs and humans separately with respective source references. In general, disease related rates were taken from existing literature on rabies epidemiology, demography and vaccination rates were estimated from (or based on distributions of) empirical data, and rates associated with processes underlying surveillance and quarantine were implied or estimated from field observations and data obtained through a longitudinal enhanced surveillance study described in detail in Chapter 3.

Parameter	Description	Value (dogs)	Value (humans)	Source (dogs)	Source (humans)
R0	Basic reproductive number	1.2	0.37	Townsend et al., 2013	Hamspon et al., 2016
k	Clumping parameter	1.33	0.56	Townsend et al., 2013	Hamspon et al., 2016
$\bar{\imath}$	Mean number of introduced cases	1.5	—	Implied	—
σ	1/Incubation period	1/22.3 days	1/40 days	Hampson et al., 2009	Warrell in Kaplan et al., 1977
γ	1/Infectious period	1/3.1 days	1/7 days	Hampson et al., 2009	Warrell in Kaplan et al., 1977
b	Per capita birth rate	0.38 per year	0.019 per year	Ferguson et al., 2015	Philippine Statistic Authority, 2016
d	Per capita death rate	0.28 per year	0.0052 per year	Estimated from data	Philippine Statistic Authority, 2016
vc/vs	Vaccination coverage/rate	Drawn from a distribution of weekly vaccination rates	1/8 days	Zero inftaled beta distribution (μ = 9.759e-03, σ = 106.682 , ϰ = 0.336)	Implied
vv	Vaccination bias	0.4†	—	Implied	—
wn	1/Duration of vaccine induced immunity	0.33 per year	—	Lakshmanan et al., 2013	—
qr	1/Duration of dog quarantine	1/14 days	—	Implied	—
μ	Probability of receiving PEP after rabies exposure	—	0.8	—	Implied
ε	Proportion of non-case patients presenting at clinics	—	Drawn from a distribution of weekly thoughput	—	Truncated normal distribution (mean = 1.259e-04, sd = 5.479e-05)
η	Probability of identifying another rabies infected dog through a follow up of rabies exposed patinets	0.7	—	Implied	—

Through computational simulations governed by the above-described stochastic model, we then investigated the impact of varying levels of quarantine on rabies dynamics under three vaccination scenarios: (1) the current estimated vaccination coverage ($\cong 30\%$), vaccination coverage reduced by 50% and vaccination coverage intensified by 50%. We tested three progressively strengthened quarantine scenarios. No quarantine was implemented under Scenario 1. In Scenario 2 we assumed only dogs identified through bite-injury patients presenting at ABTCs would be quarantined, suggesting a medium-level quarantine with an average number of dogs per patient (both non-case, and exposed case patients) around 1 (drawn from Conway-Maxwell-Poisson distribution where $q = 2.5471$ and $range = 4.3995$ for non-case patients, and $q = 2.5$ and $range = 4.3$ for exposed case patients.). (Please note that the official notation of CMP distributions is $f(x;\ \lambda, \nu)$, but here we refer to λ as q, and ν as $range$.) Under Scenario 3 we assumed a triage of bite-injury patients as per Scenario 2, but this time coupled with further field investigations/contact tracing of patient biting dogs. As such, we expected the number of dogs identified for quarantine through non-case patients to remain within the same range as in Scenario 2, but to increase for investigations informed by exposed case incidents (drawn from Conway-Maxwell-Poisson distribution again where $q = 2.8$ and $range = 1.5$). A computed distribution of the number of dogs identified for quarantine under each of the tested treatments is shown in Figure 4.3. Given the highly stochastic nature of the model, each scenario was iterated 1000 times and run over five consecutive years.

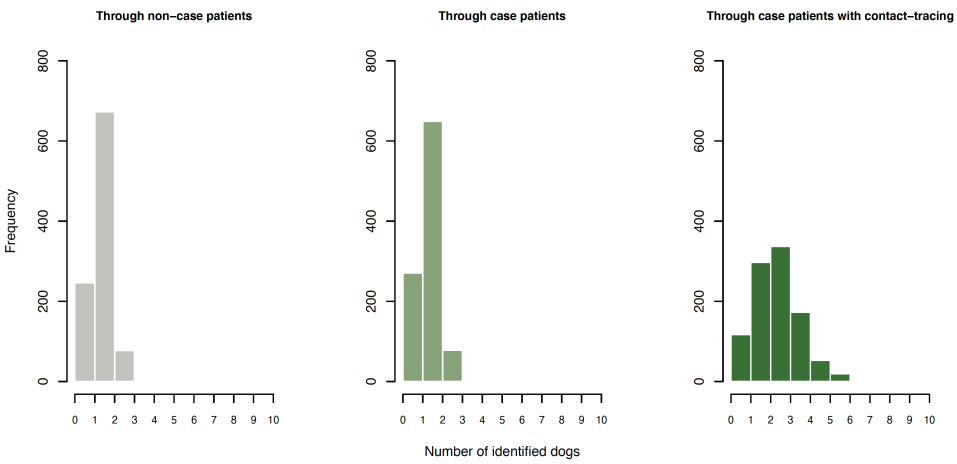

Figure 4.3: Distribution histograms for quarantine treatments. A frequency distribution of the number of dogs identified for quarantine per biting dog responsible for (form left to right) non-case

patients, rabies exposed case patients, and rabies exposed case patients coupled with additional in field contact tracing investigations of these incidents. Estimates were drawn from a Conway-Maxwell-Poisson distribution with different parameter values taken for each scenario.

4.3 Results

4.3.1 Mathematical analysis

To explore the stability properties of rabies-like dynamics when subjected to control interventions, we first found endemic equilibria of the SIRVQ (Equations 8-12) and SISVQ (Equations 13-16) models defined above.

By setting the $\frac{dI}{dt}$ equation to zero, we found the first fixed point at the endemic equilibrium to be $S^* = \frac{(\gamma+\mu+q)}{\beta}N$. This applies to both deterministic models. From here, we also derived $R0 = \frac{\beta}{(\gamma+\mu+q)}$. Thus, to ensure containment of the epidemic, the transmission rate β must be $< \gamma + \mu + q$, and the critical quarantine threshold to bring $R0$ below 1 is $q > \beta - \gamma - \mu$. Subsequently, by setting the $\frac{dV}{dt}$ equation to zero and substituting S^* for S we obtained $V^* = \frac{vcN(\gamma+\mu+q)}{\beta(wn+\mu)}$.

Making all available substitutions (i.e. $S = S^*$ and $V = V^*$) in the $\frac{dS}{dt}$ equation in the SIRVQ model we obtained $I^* = \frac{bN}{(\gamma+\mu+q)} - \frac{dN}{\beta}\left(\frac{d+wn+vc}{wn+\mu}\right)$, and by introducing I^* into the $\frac{dQ}{dt}$ equation we arrived at $Q^* = \frac{q\left[\frac{bN}{(\gamma+\mu+q)} - \frac{\mu N}{\beta}\left(\frac{\mu+wn+vc}{wn+\mu}\right)\right]}{\tau+\mu}$. Assuming disease-recovery, here $N = S + I + R + V + Q$ and $R^* = \frac{\gamma I^* + \tau Q^*}{\mu}$.

For the SISVQ model, we first defined Q^*in terms of I such as $Q^* = \frac{qI}{(\tau+\mu)}$. By substituting S^*, V^*, and Q^* into the $\frac{dS}{dt}$ equation (set to zero), we calculated $I^* = \frac{(\tau+\mu)N\ (\mu - \frac{(\mu+vc)(\mu+\gamma+q)}{\beta} + \frac{wnvc(\mu+\gamma+q)}{\beta(wn+\mu)}}{\mu(\tau+\mu+q)}$. Further simplification is possible by expressing $\frac{\beta}{(\mu+\gamma+q)}$ in terms of $R0$ which then results in $I^* = \frac{(\tau+\mu)N\ (\mu - \frac{(\mu+vc)}{R0} + \frac{wnvc}{R0(wn+\mu)})}{\mu(\tau+\mu+q)}$ and

$Q^* = \frac{qN(\mu - \frac{(\mu+vc)}{R0} + \frac{wnvc}{R0(wn+\mu)})}{\mu(\tau+\mu+q)}$. Here $N = S + I + V + Q$.

We found the Jacobian of the SIRVQ model to be defined by

$$J = \begin{pmatrix} -\frac{\beta I}{N} - \mu - vc & -\frac{\beta S}{N} & wn & 0 \\ \frac{\beta I}{N} & \frac{\beta S}{N} - \mu - \gamma - q & 0 & 0 \\ vc & 0 & -\mu - wn & 0 \\ 0 & q & 0 & -\mu - \tau \end{pmatrix}$$

with the characteristic polynomial to be

$$vc\left(-\frac{\beta Swn}{N} + wn\mu + wn\gamma + wnq + wn\lambda\right) +$$
$$(-wn - \mu - \lambda)\left[\frac{\beta^2 SI}{N^2} + \left(-\frac{\beta I}{N} - \mu - vc - \lambda\right)\left(\frac{\beta S}{N} - \mu - \gamma - q - \lambda\right)\right]. \quad (17)$$

For the SISVQ model, we found the Jacobian and its characteristic polynomial as follows:

$$J = \begin{pmatrix} -\frac{\beta I}{N} - \mu - vc & -\frac{\beta S}{N} + \gamma & wn & \tau \\ \frac{\beta I}{N} & \frac{\beta S}{N} - \mu - \gamma - q & 0 & 0 \\ vc & 0 & -\mu - wn & 0 \\ 0 & q & 0 & -\mu - \tau \end{pmatrix}$$
$$vc\left(-\frac{\beta Swn}{N} + wn\mu + wn\gamma + wnq + wn\lambda\right) +$$
$$(-wn - \mu - \lambda)\left[\left(-\frac{\beta I}{N} - \mu - vc - \lambda\right)\left(\frac{\beta S}{N} - \mu - \gamma - q - \lambda\right) - \frac{\beta I\left(\gamma - \frac{\beta S}{N}\right)}{N}\right]. \quad (18)$$

Existing models fitted to rabies time-series data suggest that the distribution of $R0$ falls predominantly between 1 and 2 (Hampson et al., 2009; Townsend et al., 2013, Kurosawa et al., 2017; Cori et al., 2018). As such, we varied transmission rate β defined as $\beta = R0 * (\mu + \gamma + q)$ by gradually increasing the value of $R0$ from 1 to 2 (where $q = 0$ to emulate baseline transmission rate under no intervention). We then set the proportion of infected dogs terminating in quarantine every week (qP) to vary between 0 to 80%, where the rate of

quarantine $q = -\log(1 - qP)/\Delta t$ and $\Delta t = 1$ (note, all parameters were expressed as weekly rates).

The vaccination rate was at first calculated from data presented in Chapter 3. By barangay, monthly vaccination coverages were averaged across the province and throughout a year giving a mean proportion of dogs vaccinated ($vcP \cong 30\%$) which was then transformed into the vaccination rate $vc = -\log(1 - vcP)/\Delta t$ where $\Delta t = 52$.

In the next step, to observe the interaction of quarantine and vaccination coverage on the system's dynamics, we set $R0 = 1.2$ (Townsend et al., 2013) and varied the yearly vaccination coverage vcP between 0 and 80% for qP ranging within the same interval.

All remaining parameters used in both models are summarized in Table 4.1, except for the rate at which infectious dogs leave the Quarantine class defined as $\tau = \frac{\gamma q}{q-\gamma}$.

For each combination of parameter values, we then calculated representative eigenvalues, the size of infected population at its endemic equilibrium, and periodicity (if applicable) at which the system – if stable – converges to its fixed points.

We found a strong trade-off relationship between the initial value of $R0$ (defining transmission rate as $= R0 * (\mu + \gamma)$) and the proportion of quarantined infectious dogs qP. For both models, increasing quarantine would eventually result in destabilizing the system and subsequent elimination of the virus. In either model, rabies did not persist for values of $R0 < 1.55$ even with no quarantine implemented (given constant $vcP \cong 30\%$). For $R0 = 1.55$ the disease would persist only if $qP = 0$. By increasing the value of $R0$ from 1.6 to 1.95 by 0.05 wide increments (equivalent to β values ranging between 2.26 and 4.53), stability of the system was subverted with quarantine levels $> 5, 15, 20, 25, 30, 35, 40$ and 40% respectively. For $R0 = 2,\ qP > 45\%$ led to a disease die out.

The values of R0 at which the disease would persist in both of the theoretical models appear marginally larger than what we would expect from empirical observations. However, the

deviation is slight and may be due to many factors such as individual differences in biting behaviour, geographical differences in the force of infection and the simplified nature of our modelling frameworks. While admittedly constricted in their predictive power, the models provide encouraging insights regarding the patterns of disease dynamics; implementing quarantine has significant potential to curtail the epidemic even in the case of low endemicity diseases such as rabies. In spite of the fact that quarantine operates only within a remarkably low fraction of the total population, its effects are likely to be seen globally.

Increasing the vaccination rate (while maintaining the average reproductive number constant as $R0 = 1.2$), led to disease elimination even at exceptionally low levels of vaccination coverage. For the disease to persist in both models, vcP would have to be $\leq 10\%, 5\%$ or no coverage at all for the qP values up to $5, 20$ and 35 % respectively. Such results are, however, purely theoretical. Ergo, they should not be considered as a quantitative representation of the system and applied directly when developing control policies. Instead, they provide a valuable qualitative evaluation of the way quarantine interplays and compliments vaccination efforts, demonstrating the prospective benefits to disease prevention when both intervention strategies are applied simultaneously.

We observed no periodicity in the SISVQ model. Increasing the value of $R0$ in the SIRVQ model led to shorter oscillatory periods, through amplifying the force of infection (i.e. $\frac{\beta I}{N}$ via increased value of β). On the other hand, increasing the vaccination coverage and/or the level of quarantine reduced the number of infectious contacts with the susceptible population, and resulted in longer periodicity. The interaction of varying parameter values with regards to periodicity is shown in Figure 4.4., and in more detail in Appendix – figures S4.1 and S4.2.

In addition, an increase in periodicity was found to be associated with a decrease in the number of infected dogs at their endemic equilibria. It is worth mentioning, that whilst showing no periodicity, the SISVQ model resulted in unrealistically large I^* values (ranging from 210 to 40,426 dogs per week). This suggests that the SISVQ structure may be unsuitable for modelling rabies beyond the accepted limitations of our deterministic models

we discussed above. Whilst the broader assumption of the SISVQ model may be justifiable, the combination of particular parameter values used here evolved into dynamics far divergent from those we would expect to occur regarding rabies transmission.

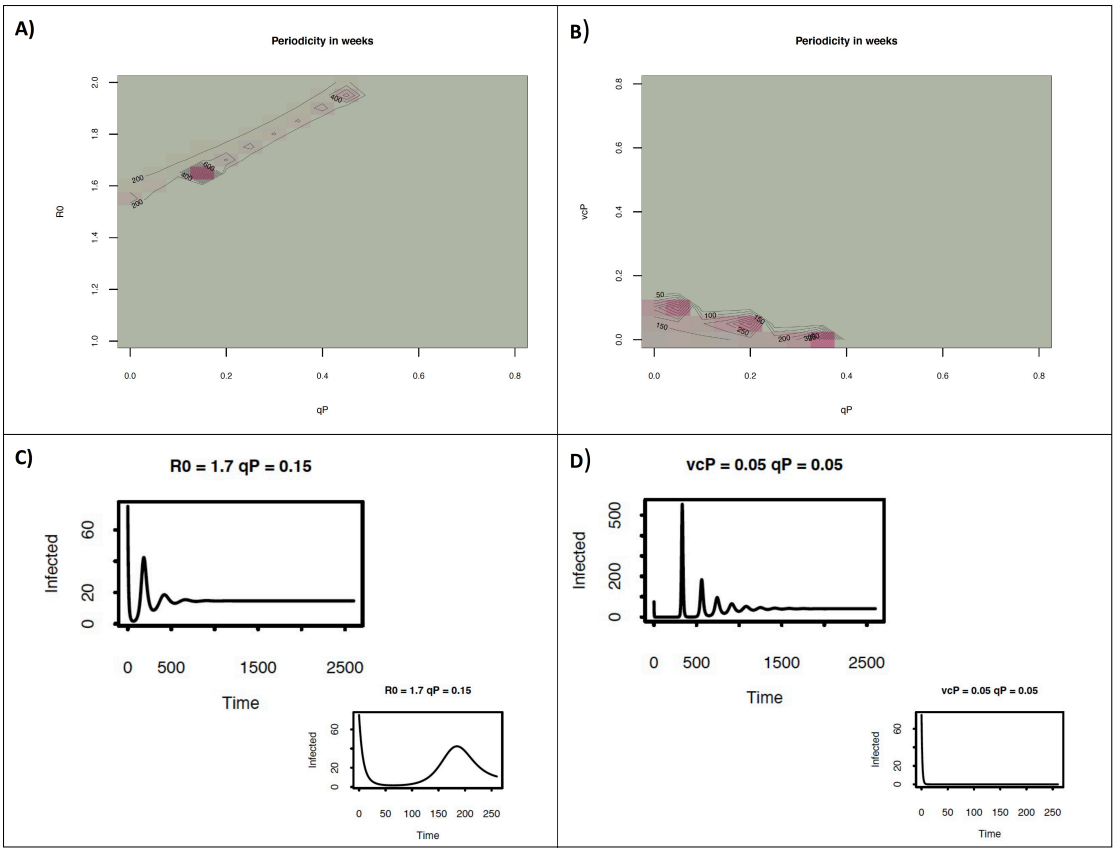

Figure 4.4: Periodicity analysis and case time series for the deterministic SIRVQ model under varying parameter values. Summary results for periodicity analysis are shown for parameter combinations in the following order: **(A)** varying $R0$ and qP (proportion of quarantined dogs) values; **(B)** varying vcP (proportion of vaccinated dogs) and qP values. Illustrative examples of periodic fluctuations in the number of infectious dogs for a particular set of parameters are shown as weekly time series over 5 (main) and 50 (inset) years: **(C)** $R0 = 1.7$, $qp = 0.15$ and $vcP = 0.3$; **(D)** $R0 = 1.2$, $qp = 0.05$ and $vcP = 0.05$. Extensive time series plots of the Infected population and joint time series of infected and susceptible dogs in the S-I phase plane drawn for all combinations of parameter values can be viewed in Appendix S4.1 (5 years long time series) and S4.2 (50 years long time series).

4.3.2 Computational analysis

Any deterministic framing, however, precludes variability in parameter values and the role of chance. For both of the deterministic models we assumed that quarantine, as well as

vaccination coverage are maintained consistently over time. We further ignored the duration of exposure which spans a wide temporal range. Symptoms of rabies in dogs usually manifest in the first month since exposure, but the incubation period may last up to months, effectively functioning as an “endogenous” incursion (Kaplan et al., 1977; Hemachudha et al., 2002). This becomes particularly relevant when we introduce constantly changing vaccination coverage associated with a build-up of susceptible dogs, consequently resulting in variability in transmission.

Moreover, stability analyses of deterministic models only consider systems at their fixed points in a closed population, and ignore the role of stochasticity with regards to the pathogen extinction and reintroduction (both locally and globally). It is the probabilistic processes that are likely most influential in shaping the future trajectories for diseases that operate at such low transmission levels. For example, the probability of a disease going extinct decreases with an increasing value of $R0$ and vice versa (Lloyd-Smith et al., 2005). As such, the deterministic threshold for elimination will be modulated by chance processes that can break individual chains of transmission resulting in a faster elimination, or allow the pathogen to persist for longer through a series of infection events and chance reintroductions in spite of an overall high level of immunity within the population.

To address the key limitations of the presented deterministic models, we modified our SIRVQ framework to account for the Removed (rather than Recovered) and Exposed compartments, temporal variability in dog vaccination and quarantine, and the impact of chance on the disease dynamics. Here we developed a stochastic discrete-time multi-species SEIRVQ model, with explicit individual biting behaviour and the probability of rabies incursions (Fig 4.2).

In line with the previous results obtained from the deterministic setting, increasing quarantine and vaccination coverage had a positive effect on curtailing the epidemic and led to significant reductions in the overall number of infections, both in humans and dogs (Fig. 4.4 and Table 4.2). However, in the stochastic formulation, neither the vaccination nor the quarantine interventions resulted in a complete interruption of transmission.

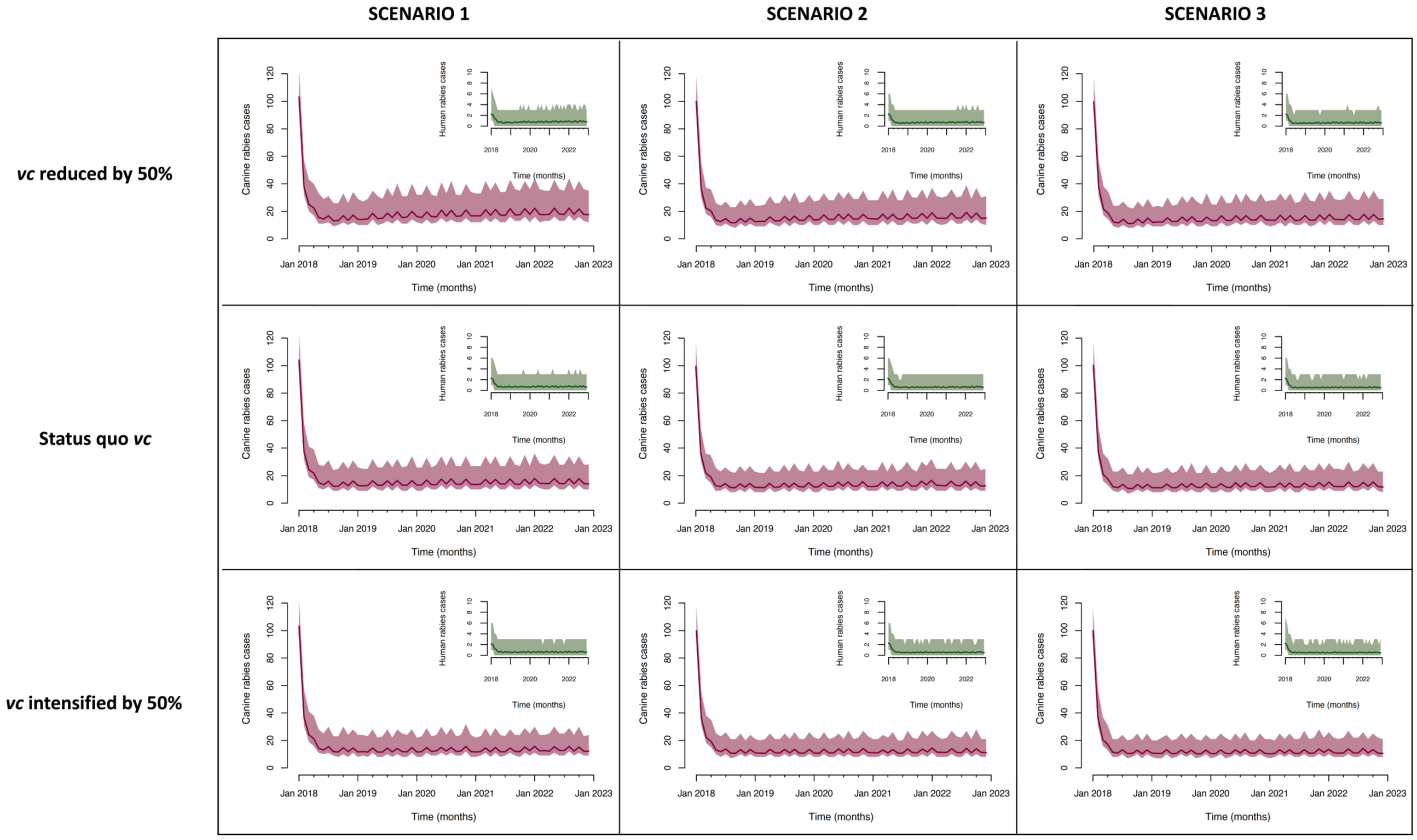

Figure 4.5: Summary time series of dog and human deaths due to rabies across different vaccination and quarantine treatments. Darker lines indicate monthly mean output values with surrounding shading indicating 95% prediction intervals (based on 1000 simulations). Whilst a dramatic decline in the case incidence is unlikely to occur for low prevalence diseases, a reduction in the number of lives saved and significantly less erratic dynamics are apparent as the gradually intensified control measures are implemented. The benefits of extensive quarantine through enhanced surveillance are particularly striking under reduced vaccination coverage, offering a largely cost-effective supplement to vaccination campaigns in resource-limited settings (see top row here and quantified in Table 4.2, or S4.3 for direct comparison between the two most marginal strategies).

We tested three levels of vaccination coverage, but even under the intensified vaccination treatment the average coverage remained relatively low (~45%). Whilst for the deterministic framework, >10% vaccination coverage was found to be sufficient in order to drive the system to extinction for $R0 = 1.2$, this threshold is likely inaccurate for a system in which the vaccination coverage changes over time as a result of variable vaccination rate,

fast turnover of susceptible individuals through high birth and death rates, and variability in the number of offspring cases for each infectious dog.

Moreover, introductions of rabies cases from outside the population pose an additional impediment to disease elimination. Exogenous incursions increase the magnitude of transmission temporarily and decrease the probability of extinction in the long term. In fact, under increased detection and quarantine of infected dogs through field investigations (Scenario 3) and the intensified vaccination efforts, endemicity appears to be sustained predominantly through incursions. Similar dynamics have been reported for diseases with lower transmission rates and/or during the endgame (i.e. pre-elimination/pre-eradication epidemiological stage as described in Barret, 2013 and Klepac et al., 2013), when heterogeneities in the force of infection (often driven by incursions) and the level of immunity may result in unpredictable stochastic outbreaks (Grassly and Fraser, 2008; Klepac et al., 2013).

Table 4.2: Reduction in the percentage of dog and human deaths across tested treatments. Column headings indicate the level of vaccination coverage. Rows summarize the percentage of dog and human lives saved comparing Scenarios 1 (no quarantine) and 2 (quarantine of dogs identified through rabies exposed case patients), and Scenarios 1 and 3 (quarantine of dogs identified through rabies exposed case patients and in field contact tracing). The percentages were calculated from totalled monthly mean output values (indicated as dark time series trajectories in Figure 4.5) computed for each of the tested treatments.

Dogs	***vc* reduced by 50%**	**Status quo *vc***	***vc* intensified by 50%**
Scenario 1 to 2	13%	9%	8%
Scenario 1 to 3	17%	13%	10%
Humans			
Scenario 1 to 2	12%	11%	10%
Scenario 1 to 3	22%	20%	15%

4.4 Discussion

Canine rabies circulating in domestic dogs represents a serious burden on public health budgets and local communities. Mass dog vaccination campaigns, the cornerstone of effective rabies control, has led to elimination of human deaths and interruption of rabies transmission at the source in most countries across the Global North (Taylor and Nel, 2015). Such campaigns, however, require systematic efforts delivered at scale and sustained over long periods of time (Townsend et al., 2013). As the availability of human and financial resources is typically limited in low- and middle-income countries, questions remain over the most effective strategies to eliminate rabies given extensive technical and structural constraints.

Contact tracing and subsequent quarantine of infectious individuals plays an important role in the control of infectious diseases at the onset of an outbreak or during the endgame (Fenner et al., 1988; Donnelly et al., 2003). Concentrating control on infected contacts can be potentially extremally cost-effective, but it relies on a sensitive surveillance system and a logistically traceable fraction of the infected population. Such conditions are typically met during the early or final stages of an epidemic when only a limited number of infections is present within the system, and for diseases with easily recognizable symptoms.

Whilst endemic, rabies provides a unique system to test a wider use of quarantine outside its traditional application. Biting behaviour is the primary indicator of rabies; transmission events, particularly from dogs to humans, are extremally memorable as often inducing severe distress or even psychological trauma. Thus, they are relatively easy to identify (when investigated) and traced back and forward as the local communities remember the bite histories long after they have occurred. In addition, rabies circulates at a very low prevalence with $R0 < 2$, indicating only a small percentage of the population is being infected at any time (Hampson et al., 2009; Hampson et al., 2016)

Using a combination of mathematical and computational models built to capture general rabies dynamics in the context of control interventions, we investigated the impact of quarantine and vaccination on the stability of the system with potential application to other low incidence diseases.

We found that in the deterministic settings even medium levels of quarantine of infected dogs posed a strong pressure on the stability of the system, and in combination with minimal vaccination efforts it would lead to a complete elimination of the disease. Analytical models are powerful tools to explore global dynamics of a system and its long-term evolution, but the insights are relevant only when assessed qualitatively. As such, the theoretical findings suggest that introducing formal quarantine into the rabies management strategies alongside mass dog vaccination campaigns would result in a reduction in the overall burden of rabies cases whilst potentially providing a critical stopgap in areas where immunity coverage falls temporarily below the optimal levels. However, the exact parameter thresholds for when elimination can be expected are only conceptual and will be modulated in empirical settings.

In fact, in the expanded probabilistic SEIRVQ framework the temporal exclusion of dogs through quarantine did not result in the pathogen elimination in spite of higher vaccination coverages than suggested by the analytical models. Stochastic extinctions of individual transmission chains offset by reintroductions of rabies from outside the population via exogenous incursions create a highly non-linear landscape of transmission, requiring more extensive efforts than predicted deterministically given the highly probabilistic nature of individual transmission events (e.g. barriers to achieving elimination of polio [Klepac et al., 2013]). Demography may also play an important role; fast population turnover due to high vital rates leads to constant restructuring of the dog population and its immunity profile. Indeed, in areas where the dog population undergoes a substantial demographic change, annual high coverage achieving (>70%) mass dog vaccination campaigns are essential to countervail the immunity loss due to removal of vaccinated dogs and their replacement with susceptible puppies (Coleman and Dye, 1996; Townsend et al., 2013).

Neither of our formulations assumed a carrying capacity of the environment. This would become a clear limitation to the deterministic models, if we decoupled the vital rates (where $b > d$), allowing for extreme population growth for higher values of $R0$. However, it is unlikely to have caused any deviations regarding patterns observed in the stochastic settings given the time frame across which we modelled the system and $R0$ being drawn

from a parametrized distribution. Moreover, depletion of the susceptible population is not associated with rabies, suggesting that changes in the size of the dog population will not affect rabies transmission unless modelled explicitly. Both empirical data and models indicate that rabies transmission between dogs occurs independently of the population density, meaning that regardless of how many dogs there in an area rabid dogs will produce on average the same number of infectious contacts (Morters et al, 2012).

Conversely, contacts leading to disease transmission are largely context specific; they will change as the interventions are being employed and in response to the phase of the epidemic curve. Social, cultural, environmental and incidental backgrounds can vary widely even across small spatial ranges, resulting in many loosely connected metapopulations that act, for most time, as individual foci (Beyer et al., 2010; Beyer et al., 2012). For diseases with higher transmission rates, smaller scale differences can be averaged across larger spatial aggregates/population, whilst for the lower incidence infections detailed spatial models provide partial leverage in capturing some of the system's heterogeneities. Extensive spatial models can, however, end up being extremely costly and inefficient if not planned through carefully. On the hunt for capturing "reality", we are in danger of formulating over-parametrized models, incapable of generating reproducible results and/or generalizable insights. The kind of models we use should be decided on with a clear understanding of the kind of questions we attempt to answer. Different structures support different types of analyses; these range from quantifying patterns (through phenomenological statistical models), testing and exploring mechanistic drivers (through deterministic mathematical models) to developing complex system predictions (through computational simulation models).

While more work begs to be done on the end of formal modelling – building frameworks that would account for the key principles of rabies transmission and the host population dynamics (pending these would be informed by a myriad of data sources, ranging from usual demographic and incidence data to more recent approaches such as bite or sequence data) – actionable guidelines and tools supported by decades of operational research are available and for the most part accessible through the Rabies Blueprint Platform (www.rabiesblueprint.org).

Our findings add onto this body of information, offering a broader understanding of the principles and effectiveness of quarantine on rabies dynamics. Implementing contact tracing and quarantine of suspect and infectious dogs may bring enormous benefits to public health, particularly in lower vaccination settings, potentially reducing the number of human deaths due to rabid bites by >20% (compared to no quarantine). However, while active investigations and quarantine appear powerful in curtailing transmission, large-scale vaccination of dogs is necessary for complete interruption of transmission of the virus and sustained elimination of rabies, given the enduring risk of re-introductions from neighbouring populations (Windiyaningsih et al, 2005; Putra et al., 2013; Bamaiyi, 2015).

Yet, early detection of incursions is critical and can preclude an undesired outbreak. With the aspiration to eliminate dog-mediated human rabies by 2030, we ought to utilize a combination of complementary control approaches, integrating and building upon operational capacities of both public health and veterinary sectors. Integrated One Health approaches of rabies surveillance have the potential to substantially increase case detection (Rajeev et al., 2020; Rysava et al., 2020) and ultimately generate vital evidence for verifying freedom from disease (Hampson et al., 2016).

CHAPTER 5

A discussion of rabies control and modelling of rabies

Whilst elimination marks the ultimate end point for most infectious disease control programmes, it also represents a major public health undertaking that requires substantial logistical and financial support as well as extensive planning and long-term commitment. Despite significant progress towards elimination targets being made in the cases of polio (Cochi et al., 2014; Bahl et al., 2018), dracunculiasis (Hopkins et al., 2020) and yaws (Asiedu, Fitzpatrick and Jannin, 2014) globally, as well as other diseases such as measles (Avila-Aguero, Camacho-Badilla and Ulloa-Gutierrez, 2015; Holzmann, Hengel, Tenbusch and Doerr, 2016), rubella (Plotikin, 2001; Andrus et al., 2011) or schistosomiasis (Bergquist et al, 2017) on a local scale, long-term persistence remains poorly characterized for most pathogens.

Canine rabies, an acute lethal infection predominantly affecting domestic dogs, provides a fascinating study system to probe mechanisms underpinning disease persistence and their implications on disease control and elimination. In theory, rabies should be easily controlled even with minimal efforts expended, given the remarkably low $R0$ and highly localized nature of transmission of the pathogen. Yet, despite its low force of infection and decades of theoretical, medical and operational research in the field, canine rabies continues to persist in low- and middle-income settings across Africa and Asia (Fahrion et al., 2017).

Concerns have been raised regarding the speed and/or duration of control programmes. Rapid elimination or control of rabies has been reported to result from synchronized delivery of high coverage-achieving vaccination campaigns in other parts of the world (Vigilato et al., 2013; Velasco-Villa et al., 2017). Such ambitious campaigns may, however, not be fully accessible to most rabies endemic countries in the Global South, given the extensive financial and human power demands associated with successful elimination initiatives. Hence, differential progress towards control and elimination targets is commonplace, constantly altering the very dynamics of the disease. As such, capturing

rabies transmission in a formal framework that would account for the highly dynamical health and political landscapes appears to be the next logical step in the future of rabies research. This, however, prompts the question of whether complex modelling structures can be built and responsibly deployed without a robust understanding of how rabies would behave if no control was implemented.

Understanding the natural mechanisms that regulate the spread of rabies remain a long-standing challenge. It is generally accepted that as the value of $R0$ remains largely unaffected by changes in the density of dog populations, rabies transmission should operate under the frequency-dependent paradigm. As such, the spread of a pathogen inducing almost 100% mortality in its host is predicted to affect a large proportion of the host population and eventually be curtailed or eliminated when the susceptible population is depleted. Such a phenomenon has, however, not been observed for rabies. In fact, rabies attack rates have been estimated to be around 1% with 0.1% of the dog population infected at any time (in rabies afflicted settings) (Mancy et al., in prep). The most recent work by Mancy et al. (in prep) reveals that both frequency- and density-dependent paradigms are possible, depending on the spatial scale of transmission. Using an exhaustive dataset of dog-to-dog transmission data collected over 14 years in northern Tanzania the authors demonstrated that the extent to which contact depends on host density changes across spatial scales, with less density-dependent behaviours observed at smaller scales. However, whilst contact was found to be largely insensitive to population density, transmission was limited by local depletion of susceptible dogs as many rabies contacts were identified as lost to already incubating (latently infected) individuals.

Mancy et al. provide ground-breaking insights into the fine mechanisms of rabies transmission; however, such a rigorous study would not be possible without exceptional amounts of work and expenses spent on the data collection end. Moreover, the modelling framework used in the study is of a complex computational nature, intractable in terms of deriving generalizable results across settings. For example, a variability in the incubation and infectious period distributions can dramatically alter the characteristics of rabies outbreaks which in turn will largely change parameter estimates for each model or setting

(Beyer et al., 2010). As such, computational individual-based models can be used to draw a comprehensive picture of a particular scenario, but they inevitably lack the robustness and generalizability of mathematical models. However, such insights into broader mechanisms of rabies transmission will likely prompt further investigations into the biological drivers of variation in individual biting behaviour beyond population-level factors, that is yet to be captured formally in a mathematical framework.

While the debate around the relationship between density and transmission will likely continue to drive much of the theoretical research, other, less complex models can provide incredibly useful insights into the prospects and effectiveness of rabies control. Chapter 4 of this thesis offered an example of a tractable way to investigate a specific question addressing the system's dynamics by applying increasingly more complex structures. We explored the straightforward concept of whether quarantine of infected dogs has the potential to reduce the burden of rabies cases and accelerate elimination targets both mathematically and computationally, focusing in particular on how and to what extent the results of the two modelling approaches differ.

While our models lack the same biological details as the existing models critiqued above (and in Chapter 1), our aim was to demonstrate that the utility of a model does not necessarily scale with its complexity when built and interpreted critically. Many models will provide only a qualitative understanding of a system, but this is not necessarily a limitation. To justify a specific intervention strategy, policy makers typically require estimates of gains and losses. Such a seemingly logical approach can, however, often result into a kind of "Catch-22" when such estimates are likely extremely loose (especially when extrapolated globally) and their making may detract from allocating resources where needed in order to overcome rabies. If the primary aim is to prevent the number of lives lost beyond figures and percentages, then instead of investing into funding a long string of indirect steps posturing as part of the solution, we need to advocate for more directed investments to ensure all exposed humans have access to a full course of PEP and that mass dog vaccination campaigns are no longer accessible only to the Global North.

Governments and international organisations repeatedly quote “lack of support and commitment from local chief executives”, together with a lack of consensus on intervention strategies and inadequate management structures, as a continued challenge to control programmes in Southeast Asia (OIE, 2016). Engagement of local communities is no doubt essential to integrated health programmes, and we too have encountered many obstacles and setbacks during our field work in Indonesia and the Philippines. However, our impression is that most conflicts come from poor communication and grossly underfunded practices, both exacerbated by deeply bureaucratic, hierarchical and often corrupt systems. For example, there is clear consensus on implementing MDV as the primary control measure in Albay, but the province is constantly facing vaccine supply constraints with some years lacking vaccines completely. On the other hand, miscommunication regarding the delayed milestones for rabies elimination in Bali sowed severe mistrust in the existing interventions and led to a persistent belief in dog culling as the most effective measure.

Researchers have repeatedly pointed out that the primary obstacle is not that local communities are simply “disengaged”, but that they lack adequate resources and power (Lembo at al., 2010; Tenzin and Ward, 2012). It is precisely in the settings with limited or ill-distributed resources that desperate solutions thrive. For example, if the dog vaccine production was not strictly proprietary, the manufacturing of a locally produced vaccine in Bali might have undergone more stringent safety and quality checks, and if profit was not the primary motivation, the impact of the vaccine might have been less detrimental or, at the very least, acknowledged and learned from. Furthermore, budgets allocated to address rabies are often considered on an annual basis (leading to *ad hoc* short-term planning), at the national level and rarely jointly between animal and public health sectors, which in the Philippines results in exponentially increasing PEP demands and costs while rabies continues to circulate at the animal source with minimal to no control implemented. This prompts the question of why local communities would engage in control and surveillance programmes when these are patchy, incomplete or non-existent, while PEP is available free of charge.

International bodies periodically deliver short-term pilot projects to demonstrate in-country presence, but rarely plan for longer-term sustainability of such programmes beyond their completion. External funding and support should be planned with a clear idea of the exact

(tangible) goals to be achieved. Such goals should then be continuously revisited along the implementation timeline and include exit steps facilitating transition of responsibilities. One Health strategies redistributing some of these responsibilities by effectively leveraging resources for longer term public health benefits are available on paper but appear to be rarely used in practice to benefit communities. With the gross disparity in access to health(care) we see around the world, One Health approaches need to be urgently taken beyond their conceptual realm and applied in practice in a sustainable and equitable fashion. In Chapters 3 and 4, we demonstrated that an intersectoral collaboration between human and animal sectors can be done at the community level and yield enormous benefits at relatively low costs, without any requirements for regulation or involvement of higher-level policy makers. Similarly, the profound success of vaccinating a vast population of dogs in Bali discussed in Chapter 2 resulted from a multi-partner engagement but was largely dependent on the enthusiasm of the local vaccination teams. There is great potential for elimination programmes to generate long-lasting impact, leaving an empowering legacy behind. However, when poorly managed, they can have completely counterproductive, damaging consequences such as stakeholder disengagement, loss of the gains initially achieved, and dire prospects for re-establishment of control programmes when commitment and trust have been lost (Barrett, 2013; Lockwood et al., 2014).

Making decisions requires values, principles and a vision of the type of society we want to live in. Whilst understanding the intricacies of rabies dynamics will require more work and offers space to diverse scientific explorations, the elimination of canine rabies is achievable with the tools already available. Disease ecologists and epidemiologists hold the responsibility of how they pitch and present their research. Whilst science should undoubtedly inform policies (where relevant), rehashing the same piece of information in the hope of shifting political values may eventually jeopardize its own principles if the relationship between scientists and policy makers is not equal.

There is a myriad of fascinating questions on the evolution and ecology of rabies. For example: (i) Finding the critical population size for maintaining rabies circulation and how this is altered by spatial connectivity and demographical processes in the dog population; (ii) Developing a better understanding of the host-pathogen co-evolution – why some species

act as a reservoir and some do not?; (iii) How does rabies epidemiology differ between species and why? Can we capture this in a formal framework?; (iv) Further stability analyses with a focus on low values of the basic reproductive number – more broadly, could timing of events be a critical determinant (e.g. Long-lived animals tend to have a lower number of offspring over their lifetime; can we draw a parallel between longevity and the length of rabies incubation period?). How to better target rabies control, however, in our opinion, is not one of them, particularly if it further delays the urgently needed political commitment.

Global targets have been set for zero human deaths from dog-mediated rabies by 2030 (WHO, 2018). With more than a century of research into the prevention and control of rabies under our belts, we now have clear recommendations, strategic plans, and safe and effective vaccines available. Yet, to this day, rabies continues to kill an estimated 60,000 people every year, of which 40% are children under the age of 15 (WHO, 2020). Canine rabies is one of the best characterized and completely preventable diseases; to reach and sustain the elimination goals now depends on the political will to collaborate and allocated adequate resources towards vaccination and surveillance.

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Appendix

S3.1 Investigation Guidelines.

BITERS DATA COLLECTION GUIDELINES

DAY 0: All cases should be considered for phone follow-up after 14 days of behavioral observation. In the instance of the bite incident being entirely provoked by the victim and the biting animal being vaccinated in the last 12 months (or exclusively kept indoors), advise the patient/animal owner to observe behavioral changes and report back should any occur. For all other cases, prompt quarantine, and for individuals classified as highly suspect, contact relevant LGU officer to prompt field investigation and sample collection.

SUSPECT: Unimmunized dogs showing no or unclear symptoms -> advise quarantine and follow-up in 14 days.

HIGHLY SUSPECT: Unimmunized dogs either exposed to, or a puppy of, a rabid individual, symptomatic dogs, dogs that died or were killed -> immediately contact the relevant LGU officer and prompt field investigation and sample collection where relevant/available.

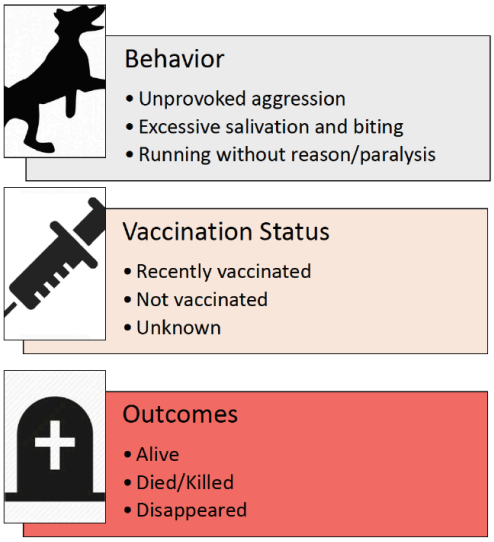
DAY 14: Conduct phone follow-up interviews with patients/dog owners for all cases classified as **suspect** or **highly suspect** cases.

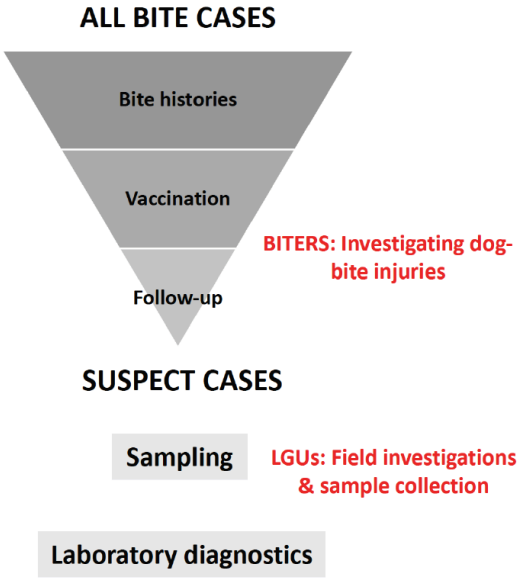
HIGHLY SUSPECT: Symptomatic individuals, dogs that bit other people or animals and individuals that died or were killed -> immediately contact the relevant LGU officer and prompt field investigation and sample collection where relevant/available.

For **offspring dog cases**, advise outbreak investigation. For **newly bitten human victims**, encourage bite victims to immediately attend ABTCs and receive post-exposure treatment.

BITERS
Bite Incidence Tool for Enhanced Rabies Surveillance

Screening of Cases





Advice for Patients

1. Prompt the dog owner to place the dog under quarantine (cage or leash) for 14 days and observe potential behavioral changes.
2. Watch out for the clinical signs of rabies.

Aggression	**Lethargy**
Restlessness	**Lack of appetite**
Hydrophobia	**Aimless running**
Drooling/excessive salivation	**Hypersexuality**
Convulsion/seizure	**Abnormal vocalization**

3. Contact your directory LGU/BITERS member if the dog shows any of the symptoms described or dies within the mandatory quarantine period.
4. Contact your directory LGU/BITERS member if the dog bites another human or animal to conduct outbreak investigation.
5. Finish your PEP regimen – don't forget to get your dose on days 0, 3, 7, and 28.
6. Remember - rabies kills, but it can be prevented by having your and your neighbors' pets vaccinated.

S3.2 Interview Forms.

Dropdown menu options are multiple choice (red), some not (blue).

PART 1: Patient profile

Category	Columns	Dropdown menu
Patient unique ID		
Clinic		
Name		
Age	Years	
	Months	
Sex		Male
		Female
Address	Province	
	Municipality/City	
	Barangay	
	Sitio	
	House number and street	
Phone contact		
Date of bite		
Date of patient presentation		
Injury type		Bite
		Scratch
		Open wound lick
		Other, specify
Body part where injured		
Number of wounds		
Bite category (WHO classification)		I
		II
		III
Treatment		None
		Washed with water
		Washed with soap

		Washed with antiseptic
		Other, specify
Other treatment		Wound bandaged
		Wound sutured
		Tandok
		Other, specify
Date PEP administered	Day 0	
	Day 7	
	Day 14	
	Day 28/30	
PEP type		IM
		ID
Immunoglobulin		Yes
		No
Patient died		Yes
		No
If patient did not receive or		

PART 2: Biting Animal profile

Category	Columns	Dropdown menu
Animal unique ID		
ID of bite victim		
Species		Dog
		Cat
		Other, specify
Age	Years	
	Months	
Sex		Male
		Female
Owner		Yes
		No
		Stray

Bite provoked		Yes
		No
Location of biting incidence		Home
		Neighbourhood/Barangay
		Other, specify
Circumstances of bite incident		
Owner		Known
		Unknown
		Community owned
		Not applicable, stray dog
Owner name		
Owner address	Province	
	Municipality/City	
	Barangay	
	Sitio	
	House number and street	
Owner phone contact		
Animal management		Pet (exclusively indoors or caged)
		Confined
		Occasionally roaming
		Free roaming/stray
Rabies vaccination status		Vaccinated within the last 12 months
		Vaccinated more than last 12 months
		Vaccinated after bite incident
		Unvaccinated
		Unknown
Animal status (on patient's Day 0 of PEP)		Healthy
		Sick
		Died
		Exposed to a confirmed/suspect rabies
		Puppy of a rabies confirmed parent
		Killed

		Disappeared
		Unknown
		Other, specify
Number of other people bitten (within		
Number of other animals bitten		

S3.3 Link to a prototype of the BITERS (Bite Incidence Tool for Enhanced Rabies Surveillance) application.

http://nero.wsbc.warwick.ac.uk/biters/

S4.1 Five-year time series plots of Infected population and joint time series of Infected and Susceptible dogs for SIRVQ model.

A) Varying the value of $R0$ and qP.
https://drive.google.com/file/d/1vT2CBYK1Rz6qNYr_LfdJ4WBisCm579xB/view?usp=sharing

B) Varying the value of vcP and qP.
https://drive.google.com/file/d/1QkE4vt9BiQYaReIIZ1inBCZnN4ouzk_B/view?usp=sharing

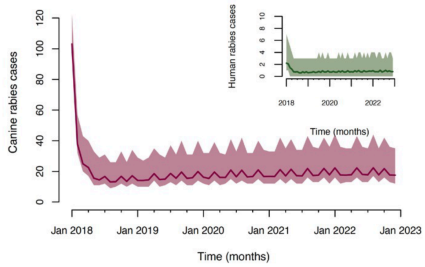
S4.2 Fifty-year time series plots of Infected population and joint time series of Infected and Susceptible dogs for SIRVQ model.

A) Varying the value of $R0$ and qP.
https://drive.google.com/file/d/17LnwZ5cCVNQR5i20rvq5XvM6OC2JO3pI/view?usp=sharing

B) Varying the value of vcP and qP.
https://drive.google.com/file/d/1dnf-Xam6mjnjliG1TjU66loJBgr65Bz4/view?usp=sharing

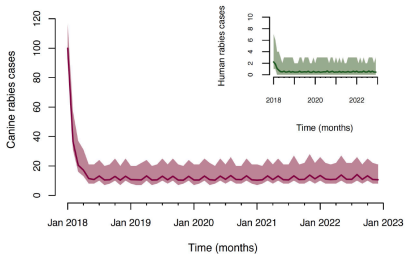
S4.3 Direct comparison of rabies dynamics – represented by human and dog deaths due to rabies – between two most marginal scenarios tested. The top descriptions indicate the level of surveillance with "status quo" referring to the current practice of no patient triage and filed investigation. Bottom descriptions indicate the level of vaccination coverage where low and high coverage reach 30% and 45% respectively.

status quo



Low vaccination coverage settings

IBCM + contact-tracing



High vaccination coverage settings