

DATA AND MODELING TO INFORM CANINE RABIES
CONTROL AND ELIMINATION

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Abstract

Canine rabies is responsible for an estimated 60,000 human deaths annually across the globe. These deaths are entirely preventable, either through mass dog vaccination or by post-exposure vaccination of humans, and the World Health Organization and its partners have set a goal of zero human deaths due to canine rabies by the year 2030. My dissertation uses two different methodologies, field epidemiological studies and mathematical modeling, to answer questions of how we can improve control and surveillance for canine rabies. Chapters 1 and 2 of my dissertation focus on epidemiological studies of rabies in Madagascar. In Chapter 1, I describe the results of my project in collaboration with in-country partners (the Ministry of Health, the Department of Veterinary Services, and the Institut Pasteur de Madagascar) to collect baseline data on rabies incidence in animals and rabies exposures and deaths in humans, and to test better methods for surveillance in the Moramanga District, Madagascar. In Chapter 2, I use this dataset and other data on patients seeking care for animal bites in Madagascar to estimate how geographic accessibility to the human rabies vaccine drives the burden of rabies spatially, and to explore how improving accessibility could mitigate this burden. In the second half of my dissertation, I look more broadly at how transmission modelling of canine rabies can be applied to answer critical questions regarding rabies control. In Chapter 3, I critically review the existing modeling literature, identify gaps in the current methods, and propose new ways forward for how modeling can contribute to rabies control. In Chapter 4, I use fine scale spatial and temporal data on rabies cases in the Serengeti District, Tanzania to test dynamic models of rabies transmission and identify key features of transmission and control necessary to recapture dynamics. Overall, this work brings forth a set of epidemiological and quantitative toolsets that can be used to tackle key challenges on the road to global rabies elimination.

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Introduction

Disease elimination is an elusive goal that requires technical knowledge and practical implementation to be realized. To date only one human and one animal disease have been successfully eliminated through coordinated control efforts, smallpox and rinderpest, respectively [1]. Critically, integrating key aspects of the pathogen epidemiology and understanding features of transmission were likely key to achieving this success [2].

Mathematical models are a powerful tool in the elimination arsenal and, combined with epidemiological studies, can help to develop ‘best-bets’ for control strategies [3]. Models can shed light onto the factors that drive disease dynamics, such as seasonality or age contact patterns; they can be used to estimate burden and costs of interventions; they can forecast future dynamics and also explore potential outcomes given different control and transmission scenarios. But it is also critical that models are grounded in data that are representative of the lived reality of people affected by a disease.

Canine rabies causes an estimated 60,000 human deaths annually, primarily in low and middle income countries in sub-Saharan Africa and Asia [4]. These deaths are entirely preventable: human deaths can be prevented through prompt post-exposure prophylaxis (PEP) and transmission can be interrupted in domestic dogs through mass dog vaccination. A target for zero human deaths due to dog-mediated rabies by 2030 (ZeroBy30) has been set by global health partners through implementation of a combination of these interventions [5]. At this critical policy juncture, research on intervention strategies and policy can greatly inform the path to elimination. Surveillance for canine rabies in endemic contexts is highly limited and available data are often restricted to urban and suburban centers with greater access to diagnostics and veterinary services [6]. In Chapter 1, I tackle this issue in a district in Madagascar, setting up a clinic based surveillance study to assess rabies burden and surveillance. I find that rabies burden and cases are significantly underreported in the district, and use estimates of exposure incidence and health-seeking behavior to estimate burden. In Chapter 2, I integrate data collected from this study with routine public health data from across Madagascar to incorporate spatial access to PEP into estimates of human rabies burden and explore how expanding access to PEP can mitigate this impact, particularly in the context of a potential investment by GAVI

in supporting countries to expand access to PEP.

In Chapter 3, I review the existing body of dynamic transmission modeling work for canine rabies and identify key gaps and issues: primarily the paucity of data and of modeling studies that fit to data and the lack of a modeling framework which generates dynamics consistent with both endemic and epidemic dynamics. Finally, in Chapter 4, I tackle this gap by developing a simplified individual based model of canine rabies transmission, and fitting the model to a comprehensive long-term dataset of canine rabies cases and dog vaccination from the Serengeti District. I find that incorporating both the spatial scale of population mixing and the scale of control are critical to generating dynamics consistent with observed data, and with expectations in an endemic context. Overall, this work contributes in a multi-faceted way to tackling a pressing public health issue, both by generating key data and developing new quantitative approaches to taclking how best to control, and eventually eliminate canine rabies.

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Chapter 1

Healthcare utilization, provisioning of post-exposure prophylaxis, and estimation of human rabies burden in Madagascar

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Minor formatting modifications and edits have been made for the dissertation.

1.1 Abstract

In Madagascar, dog-mediated rabies has been endemic for over a century, however there is little data on its incidence or impact. We collected data over a 16-month period on provisioning of post-exposure prophylaxis (PEP) at a focal clinic in the Moramanga District and determined the rabies status of biting animals using clinical and laboratory diagnosis. We find that animal rabies cases are widespread, and clinic-based triage and investigation are effective ways to increase detection of rabies exposures and to rule out non-cases. A high proportion of rabies-exposed persons from Moramanga sought (84%) and completed PEP (90% of those that initiated PEP), likely reflecting the access and

free provisioning of PEP in the district. Current clinic vial sharing practices demonstrate the potential for intradermal administration of PEP in endemic African settings, reducing vaccine use by 50% in comparison to intramuscular administration. A high proportion of PEP demand was attributed to rabies cases, with approximately 20% of PEP administered to probable rabies exposures and an additional 20% to low-to-no risk contacts with confirmed/probable animal or human cases. Using a simplified decision tree and our data on rabies exposure status and health-seeking behavior, we estimated an annual incidence of 42–110 rabies exposures and 1–3 deaths per 100,000 persons annually. Extrapolating to Madagascar, we estimate an annual burden of 282–745 human rabies deaths with current PEP provisioning averting 1499–3958 deaths each year. Data from other clinics and districts are needed to improve these estimates, particularly given that PEP availability is currently limited to only 31 clinics in the country. A combined strategy of mass dog vaccination, enhanced surveillance, and expanded access to PEP along with more judicious guidelines for administration could effectively reduce and eventually eliminate the burden of rabies in Madagascar.

1.2 Introduction

To date, canine rabies is estimated to cause around 60,000 human deaths annually [1]. Infection is completely preventable if exposed individuals receive prompt post-exposure prophylaxis (PEP), but most human cases occur in low-income countries in Africa and Asia, where access to PEP is often limited [2]. Mass dog vaccination has proved effective in preventing human rabies in many countries [3]. The WHO and their partners have set a target for an end to human deaths due to dog-mediated rabies by the year 2030 [4]. This goal will require delivering vaccine interventions in both domestic dog and human populations in resource-limited settings where canine rabies remains endemic.

In Madagascar, the first human rabies case was reported in 1896. The Institut Pasteur de Madagascar (IPM) has provided PEP free-of-charge to patients in the country since 1902 [5]. Until 2006, IPM provided rabies nerve-tissue vaccines to all district health centers. In 2006, use of nerve tissue was discontinued in the country, and shifted to use of the Purified Vero Cell Rabies Vaccine solely, but with provisioning to only a subset of district health centers [6]. Currently, there are 31 anti-rabies medical centers (ARMC, also referred to as Centre de Traitement Antirabique) across the country. Each ARMC is located in a public hospital or health care center, and there are no other sources of PEP available publicly or privately in the country. At the time of the study, all ARMC were using the modified Thai Red Cross (TRC) protocol (i.e. 2 intradermal injections of 0.1 mL at two sites, deltoids and/or thighs, on days 0, 3, 7 and 28). Purified equine rabies immunoglobulin (RIG) is only available at the IPM ARMC in the capital city Antananarivo, and patients from peripheral ARMC are supposed to be referred to the capital when RIG is necessary. Both vaccine and RIG are

administered free-of-charge to patients. Culling is the official policy to respond to any suspected or confirmed animal rabies case (Decret No. 95-375, 1995) and dog vaccines are limited in availability and only at a high cost to owners.

As rabies control in the dog population is minimal and ad hoc, and PEP availability is limited to the 31 ARMCs, there is likely a significant burden of rabies in Madagascar. The National Rabies Reference Laboratory (NRRL) at IPM in Antananarivo is the only facility with the capacity for rabies diagnostic testing [5] and most of the samples submitted to the laboratory come from the capital city and surrounding peri-urban areas. Even with this limited surveillance, 62% of submitted animal samples tested positive for rabies between 2010 and 2015 [7], with cases of canine rabies having been recorded in 38 out of the 114 districts in the country [6]. Annually, between 4 and 10 human rabies cases and 21-111 animal rabies cases are laboratory confirmed [7], but underreporting of both human and animal cases is likely substantial.

To better understand the burden of rabies in Madagascar and PEP functioning in this context, we collected data on reported animal bites and vaccine provisioning at the ARMC in the Moramanga District over a 16-month period (Sep 2016–Dec 2017). We followed up on bite patients to assess the rabies status of biting animals through clinical and laboratory diagnosis and contact tracing to identify unreported exposures. Using the resulting estimates of health seeking behavior, PEP provisioning and adherence, and the incidence of rabies exposures, we applied a simplified decision tree to estimate the number of deaths averted and the current burden of human rabies in the Moramanga District and extrapolate this across Madagascar.

1.3 Methods

1.3.1 Study site

The Moramanga District is located mid-way between the central highlands and the east coast of Madagascar, at an average altitude of 936m. It comprises 21 communes, covering approximately 7150 km² with a human population between 300,000–350,000 people (www.worldpop.org, [8]). The Moramanga ARMC is located in the Emergency Room (ER) of the District Hospital. The clinic uses 0.5 mL vials of Verorab (Sanofi Pasteur) anti-rabies human vaccine provided through IPM. Generally, if a vial is opened, it is used within one working day. The ER staff requests that patients report between 9 AM–2 PM for PEP to facilitate vial sharing, with one vial split between two patients. Whether animal bites are treated as emergencies and given PEP after these hours depends on the on-call physician. Patients first reporting to other public or private hospitals depend on clinician referral to report to the ARMC. The nearest other health facility offering PEP is the IPM ARMC

in Antananarivo, which is a minimum of 2–3h travel time from anywhere in the district. Patients requiring RIG are referred to IPM.

1.3.2 Data and analyses

From September 2016 to December 2017, we collected baseline data from clinic registers on PEP administration and patient throughput, including patient demographics. The clinic does not track vial use, so we calculated a conservative minimum estimate of vaccine waste (i.e. not accounting for errors in administration, breakage etc.), based on incomplete vial sharing. Current practice is for a single 0.5 mL vial to be split between two patients, with each receiving 0.2 mL of vaccine (2×0.1 mL injections/visit), and the remaining 0.1 mL of vaccine considered wastage. We assumed a further 0.2 mL is wasted on each day with an odd number of patient presentations (for vials used only by one patient, with the remaining 0.3 mL discarded). We also calculated the minimum estimate of vials required and wastage under alternative scenarios: with 5×0.1 mL injections obtained per 0.5 mL vial; adopting the newly recommended abridged 1-week ID regimen administered on day 0, 3, and 7; and adopting these two practices in combination. We compared these scenarios to the minimum number of vials necessary given intramuscular (IM) administration (Essen 4-dose or Zagreb) with one vial used per injection and assuming no change in compliance.

For all patients, the clinic collects data on the biting animal species and compliance to PEP, but not on which patients are referred and/or receive RIG. We used data from patients who were either bitten or resided in Moramanga that reported to the IPM ARMC during this period to identify those that received RIG, although we did not have data for how many were referred in total. For a subset of biting animals, samples were collected either by local veterinary surveillance officers submitting the whole head or animal for testing) or using the straw method for brain tissue collection [9]. Samples were sent to the NRRL at IPM for diagnostic confirmation using the fluorescent antibody test (FAT). Probable human rabies cases were identified from patients who presented to the clinic with neurological signs, had a history of an animal bite, and died shortly after, or deaths reported to the district health office also with consistent history. One suspect human case was confirmed (positive RT-PCR result on a skin biopsy from the neck [10]).

We interviewed as many patients as possible to classify their rabies exposure status. We classified animals and people (in terms of their exposure to rabies), according to the following case definitions: - Confirmed case/exposure: an animal or human that tested positive (by FAT or RT-PCR, respectively) for rabies/a person bitten or scratched by an animal that tested positive for rabies.

- Probable case/exposure: an animal or human that was classified as probable for rabies/a person

who was bitten or scratched by an animal that was classified as probable for rabies based on adapting the six-step method, with probable cases defined as showing at least one clinical sign and dying or disappearing within 10 days of the bite [11].

- Contact with a confirmed/probable rabies case: any person in contact with a confirmed/probable human or animal rabies case as defined by the current national guidelines for ARMCs:
 - Touching the mouth or saliva, or sharing food and drink (human case).
 - Manipulating the body or helping to bury (human case).
 - Licks or contact with the saliva 15 days preceding death (human or animal case).
 - Taking a sample from a suspect animal or human case.

For the majority of these patients, the type of contact was not recorded at the clinic. - Non-case/non-exposure: an animal that was determined to not be rabid/ a person who was bitten or scratched by an animal that was determined to not be rabid (i.e. an animal that remained alive 10 days after the bite or tested negative).

- Unknown case/exposure: an animal/patient for whom we were unable to assign a status to, either due to ambiguity in the case history or who, despite attempts via phone call or household visit, we were unable to locate.

For patients reporting between Sep 2016–July 2017, we verified the status of the animal retrospectively through phone interviews or household visits. From August 2017 until December 2017, we interviewed patients directly at the clinic and triaged patients for follow-up, only conducting household visits for cases assigned as probable rabies or for those we were unable to interview at the clinic. Household visits were also limited by accessibility due to road conditions.

We adapted established decision tree frameworks [1], [12] to estimate the burden of human rabies and deaths averted through use of PEP using parameters derived from these data. We assumed that no deaths resulted from incomplete or delayed PEP, including the absence of RIG, and that all people who report to an ARMC receive PEP, i.e. no shortages or vaccine refusal. We excluded contacts with (rather than exposures to - see case definitions above) confirmed/probable cases from this analysis, as these pose minimal to no risk of infection [13]. We calculated human rabies deaths and deaths averted by PEP according to the decision tree described in Fig. 1, where prabid is the proportion of reported bites that are considered rabies exposures (due to confirmed/probable rabid animals), preport is the proportion of rabies exposures that present to an ARMC, and p_{infect} is the probability of infection, and thus death, given a rabies exposure [14]. We calculated an annual bite incidence in the district by taking the average monthly bites per 100,000 recorded in our data

during the period of systematic triage (Aug 2017–Dec 2017) and multiplying by 12. Population estimates were taken as the midpoint between 2015 and 2020 UN adjusted population projections from World Pop (www.worldpop.org, [8]). All data were collected using tablets (Samsung Tab 4 and Tab A) using forms from the Wise Monkey Portal (<http://www.wisemonkeyfoundation.org/>) and the Device Magic application (<https://www.devicemagic.com>), and associated data were submitted and stored in secure cloud-based servers. All data analysis and figures were done in R (version 3.5.0, R Core Team, 2018).

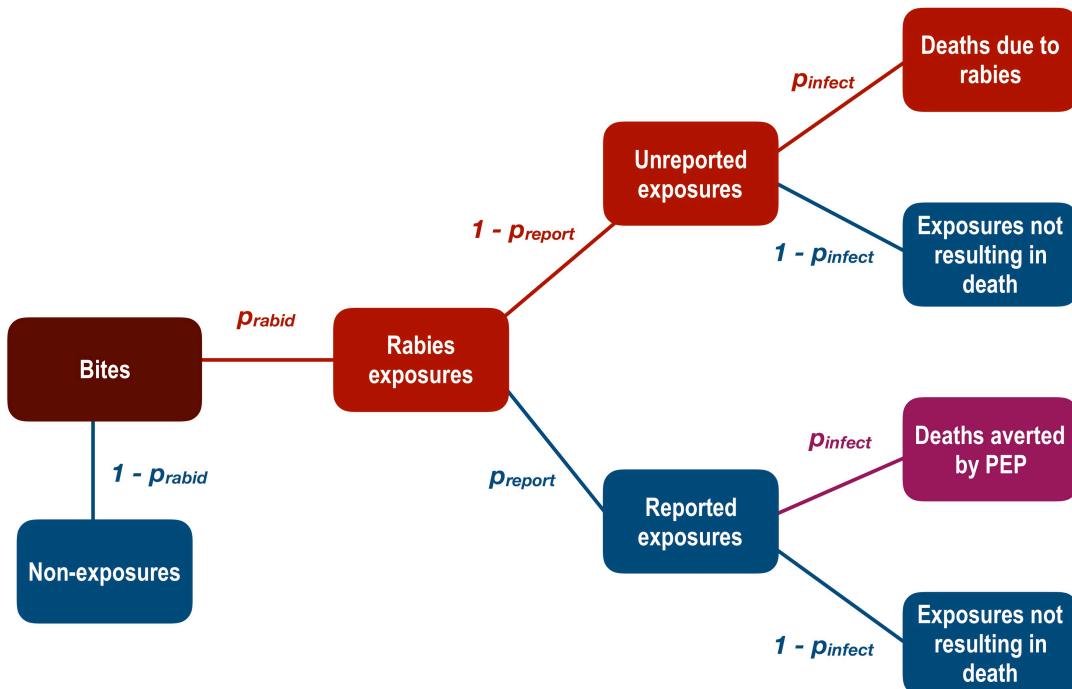


Fig. 1. Adapted decision tree framework to estimate burden of human rabies deaths and deaths averted by PEP. We considered that some proportion of total bites in the population (expected bites annually, dark red box) are genuine rabies exposures ($\text{Bites} \times p_{\text{rabid}} = \text{Rabies exposures}$), and non-exposures ($(1 - p_{\text{rabid}}) \times \text{Bites}$) do not contribute to rabies deaths or averted deaths. Of the genuine rabies exposures, a fraction present to an ARMC and all of these persons receive PEP ($\text{Rabies exposures} \times p_{\text{report}} = \text{Reported exposures}$). Some of these exposed persons would otherwise have become infected and died if they had not received PEP ($\text{Reported exposures} \times p_{\text{infect}} = \text{Deaths averted by PEP}$). Of the unreported exposures, a proportion will die due to rabies infection ($\text{Unreported exposures} \times p_{\text{infect}} = \text{Deaths due to rabies}$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

1.3.3 Ethics statement

This research was approved by the Princeton University IRB (# 7801) and the Ministry of Public Health Ethics Committee (# 105-MSANP/CE). Oral informed consent was obtained from all interviewed participants. Sample collection from animal carcasses was approved through the Princeton University Institutional Biosafety Committee (# 1105-16) and the Animal Use and Care Committee (# 2079A-16).

1.4 Results

1.4.1 PEP provisioning at the clinic

Between September 2016–December 2017, a total of 1019 patients reported to the ARMC. Multiple patients were likely to present on a given day, with only 3% of days where a single patient reported. On average, 7 patients presented per day, but this distribution was skewed with 10 or more patients reporting on 22% of days, and zero patients on only 7% of days (Fig. 2A). Using the updated TRC regimen, an estimated 1927 vials (of 0.5 mL) were required over the study period given the observed daily throughput of ARMC patients. Current ID administration requires approximately 50% less vaccine vials compared to an IM regimen (3597 vials) (Fig. 2B). Use of the abridged 1-week ID regimen could reduce vial use by 20% and drawing 5 × 0.1 mL injections per vial rather than 4 would further reduce vial use by up to 31%. In general, extracting 5 × 0.1 mL injections from a vial reduces the volume of vaccine wasted by 40–50% (Fig. 2B).

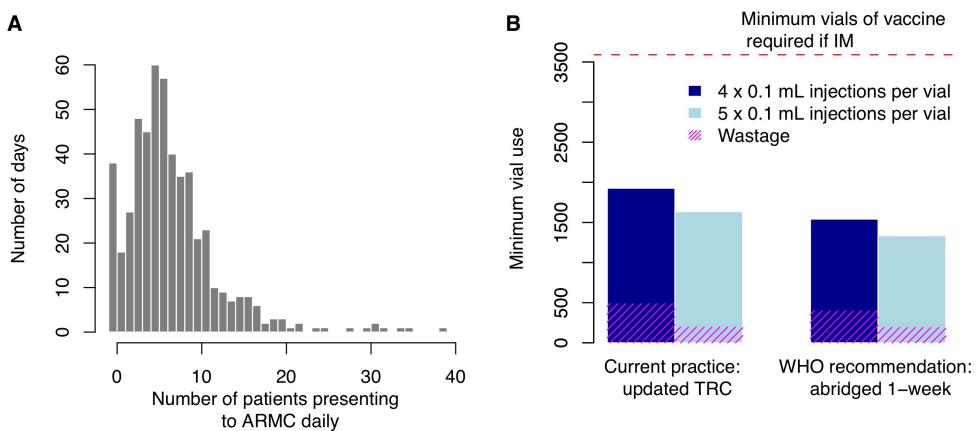


Fig. 2. PEP administration and vaccine use. (A) Distribution of observed daily patient presentations (i.e. the number of days with N patients reporting to the ARMC) and (B) calculation of the minimum

volume of vaccine (mL) used under current practice with PEP administered according to the updated TRC regimen or according to the latest WHO recommendations with the abridged 1-week ID regimen. Use of 4×0.1 mL per 0.5 mL vial (current practice) vs. 5×0.1 mL injections per 0.5 mL vial were also compared. The red dashed line corresponds to vaccine use under IM administration, assuming 1 vial per IM injection and the same level of compliance (i.e. under the Essen 4-dose or Zagreb regimen). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

1.4.2 Rabies status and characteristics of biting animals

Of the 704 biting animals that were identified at the clinic and through contact tracing, domestic dogs made up the majority (87.5%), followed by cats (9%). Other species (<4% of biting animals) included cows, rodents, one lemur, and one bat. The majority were owned animals (56.7%). We followed up on 390/704 of these animals and identified that 67 were probable cases and 19 were confirmed cases, responsible respectively for 88 probable and 32 confirmed human exposures (Table 1, Fig. 3). Almost all of these confirmed/probable rabid animals were domestic dogs (76/87). Rabies was widespread, with confirmed/probable cases detected in 14/21 communes in the Moramanga District (Fig. 3A). In addition, there was at least one confirmed case in 11/16 months and at least one probable or confirmed case detected in each month of the study. There were also 4 human cases (1 confirmed, 3 probable) reported in the district during this period (Fig. 3B).

Table 1. Characteristics of biting animals as recorded from follow-up investigations.

	Confirmed (%)	Probable (%)	Unknown (%)	Non-case (%)
Total	19	68	108	195
Species				
Cat	3 (15.8)	2 (2.9)	9 (8.3)	21 (10.8)
Dog	15 (78.9)	61 (89.7)	91 (84.3)	173 (88.7)
Bovine	1 (5.3)	5 (7.4)	0 (0)	1 (0.5)
Rodent	0 (0)	0 (0)	6 (5.6)	0 (0)
Owned animal	16 (84.2)	42 (61.8)	30 (27.8)	189 (96.9)
Vaccinated	0 (0)	0 (0)	9 (8.3)	57 (29.2)

	Confirmed (%)	Probable (%)	Unknown (%)	Non-case (%)
Veterinary observation	3 (15.8)	5 (7.4)	4 (3.7)	68 (34.9)
Outcome				
Alive	0 (0)	0 (0)	14 (13)	186 (95.4)
Disappeared or unknown	0 (0)	17 (25)	81 (75)	0 (0)
Died due to disease	4 (21.1)	19 (27.9)	0 (0)	1 (0.5)
Killed after biting a person/animal	14 (73.7)	23 (33.8)	4 (3.7)	2 (1)
Other cause of death	0 (0)	9 (13.2)	2 (1.9)	6 (3.1)
Clinical signs				
Bit multiple people	11 (57.9)	26 (38.2)	0 (0)	10 (5.1)
Bit other animals	5 (26.3)	10 (14.7)	1 (0.9)	0 (0)
Observed source of infection(i.e. signs of previous bite/observed bite)	4 (21.1)	5 (7.4)	2 (1.9)	2 (1)
Unprovoked aggression	12 (63.2)	47 (69.1)	41 (38)	33 (16.9)
Excess salivation	6 (31.6)	14 (20.6)	3 (2.8)	2 (1)
Hydrophobia	1 (5.3)	1 (1.5)	0 (0)	0 (0)
Lethargy	2 (10.5)	7 (10.3)	0 (0)	0 (0)
Paralysis	1 (5.3)	5 (7.4)	0 (0)	1 (0.5)
Vocalization	3 (15.8)	4 (5.9)	0 (0)	1 (0.5)
Restlessness	3 (15.8)	0 (0)	0 (0)	0 (0)
Hypersexuality	0 (0)	0 (0)	0 (0)	0 (0)
Running no reason	4 (21.1)	7 (10.3)	0 (0)	0 (0)
Strange movement	2 (10.5)	8 (11.8)	1 (0.9)	1 (0.5)
Provoked bite*	5 (26.3)	10 (14.7)	24 (22.2)	57 (29.2)
Average number of animals bitten	0.313	0.236	0.019	0
Average number of humans bitten	2.06	1.73	1	1.05

- With at least one indication of provocation (i.e. hitting or kicking the animal, interaction with food or object, playing or running, entering the house of the owner with a guard dog, history of habitual aggression).

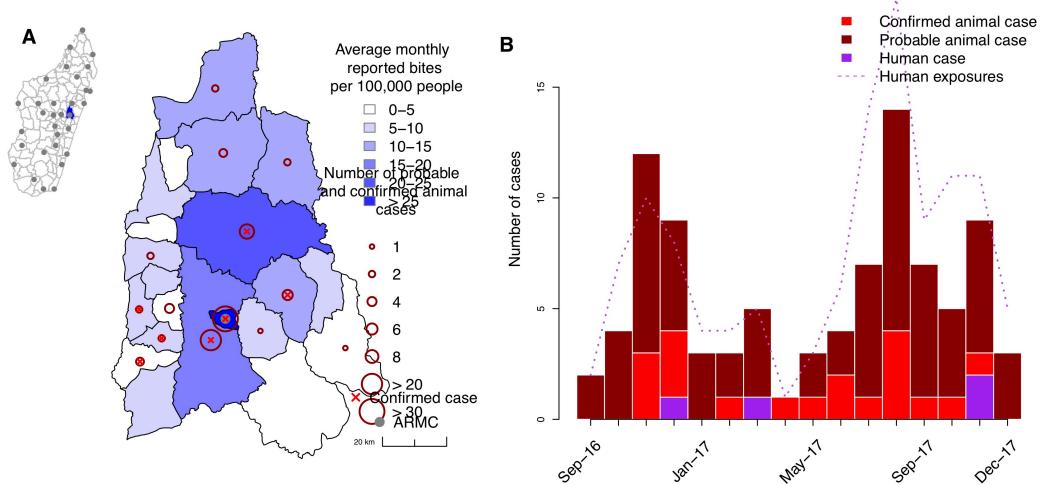


Fig. 3. Rabies in the Moramanga District. (A) Average monthly reported bite incidence (blue shading) per commune and total numbers of probable or confirmed cases (dark red circles). A red \times indicates if at least one animal case was confirmed in the commune. All coordinates are the commune centroid, and the inset shows the district (in blue) in relation to the other districts (polygons) and ARMC (grey points) in Madagascar. (B) Time series of probable and confirmed animal cases and human cases (bars), as well as total confirmed/probable rabies exposures (dashed line) from September 2016 to December 2017. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Amongst probable and confirmed animal rabies cases, unprovoked aggression was the most common clinical sign followed by excessive salivation; other clinical signs were observed less frequently (<15% of probable/confirmed cases). Confirmed and probable animal cases were more frequently involved in biting multiple people (42.5%) than non-cases (5.4%). They also more frequently bit several animals. In contrast, provoked bites were twice as common amongst non-cases (Table 1). Generally, clinical signs were noted for both non-cases and probable cases, and bites from a probable animal could also be classified as provoked based on our criteria (so could not be used to rule out rabies). A source of infection was only identified for nine confirmed or probable cases (i.e. either an observed bite or signs of a bite prior to biting or the onset of clinical signs). Owners or community members rarely observed when rabid animals bit other animals.

Most probable or confirmed rabid animals were killed after biting or attempting to bite people or other animals (42.5%), or died from disease (26.4%) or other causes (10.3%, including being hit by

car, poisoned, or dying from injuries). The remaining 18.6% disappeared after the bite. The majority of animals classified as non-cases were alive 10 days after the bite (94.4%), but three animals that were not alive within 10 days of the bite subsequently tested negative, and eight died at a later date (>10 days after the bite, Table 1).

Of the animals we investigated, 20.5% were reported to have been placed in veterinary observation. Seven of these 80 observed animals were considered to be probable rabies cases by the veterinarian. However, we did encounter two cases where the veterinary conclusion differed from our case determination (one probable case that was declared a non-case by the veterinary officer due to the age of the animal, i.e. <3 months, and the other that was alive at the time of our investigation approximately 3 months after the bite case, which was declared a suspected rabies case by the veterinary officer at the time of the visit). 17% of the animals we investigated were reported to be vaccinated, with 29.2% of non-cases and 28.7% of those placed in veterinary observation reported to be vaccinated. No probable or confirmed animals had a history of vaccination.

1.4.3 Exposure status, health-seeking behavior, and PEP compliance of bite victims and patients reporting to the ARMC

Of the 1019 patients presenting to Moramanga AMRC, 1.5% were in transit and only completed a subset of doses at the clinic. A further 6.8% came from outside of the district but completed their PEP course in Moramanga; these mostly came from the neighboring district of Anosibe An'Ala (41/63), which does not have an ARMC and is a minimum of 12h travel time from the Moramanga ARMC. Twelve patients were bitten outside the District, but resided in Moramanga and completed their PEP course at the ARMC. We excluded patients bitten in other districts from further analyses.

Excluding contacts with a confirmed/probable case (N = 197), we were able to classify the status of 41.1% of human exposures over this 16 month period, however this proportion varied over time. By conducting clinic-based triage, we were able to classify double the proportion of bite patients to a known exposure status (27.4% of patients pre-August 2017 vs. 61.4% post-August 2017, Fig. 4A). Of the 399 patients we followed up with, we were unable to assign an exposure status to 25.8% (i.e. ‘Unknown’).

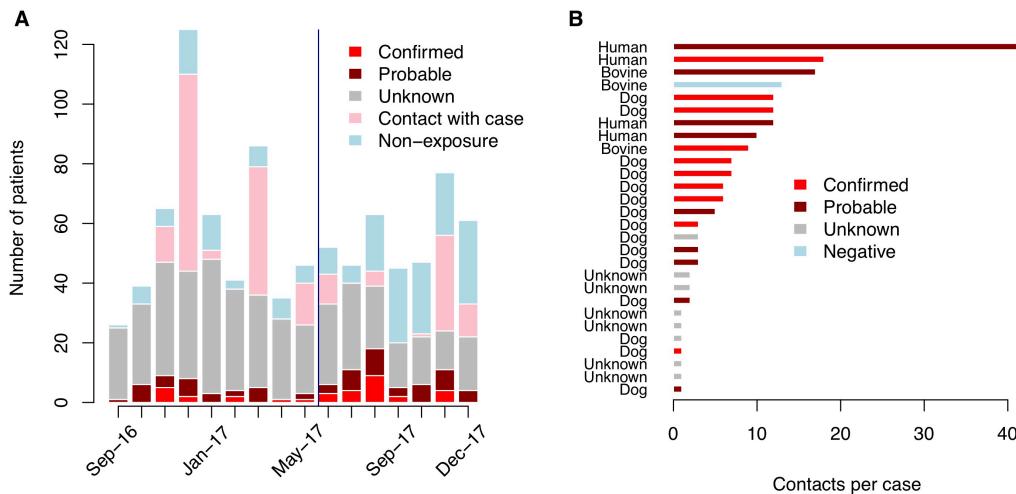


Fig. 4. Patients reporting to the ARMC. (A) Monthly time series of patients reporting to the ARMC by their exposure status; the blue line indicates when systematic triaging of patients at the clinic began. (B) Number of contacts per probable case and the rabies status of the case (one bovine case tested negative after sample submission). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Reporting delays were on average 2.8 days for probable exposures and 1.5 days for confirmed exposures, with 61.1% of patients reporting within 2 days of the exposure overall (Table 2). Overall PEP completion was high, with 89.7% of patients completing at least 3 doses (88.1% of probable or confirmed rabies exposures). Approximately 1.7% of patients completed more than 4 doses, as clinic protocol was to restart the course if there was a delay between PEP doses. Eighteen patients from the Moramanga District were recorded at IPM, and fourteen of these patients received RIG (4 confirmed, 3 unknown, and 7 non-exposures).

Table 2. Characteristics of all patients reporting for PEP and additional bite victims identified through contact tracing, including the type of exposure and health seeking behaviour.

	Confirmed (%)	Probabal (%)	Unknown (%)	Non- exposure (%)	Contact (%)
Total	35	85	425	202	197
Average age	23.5	23.8	23.7	25.5	30.7
Male	27 (77.1)	50 (58.8)	250 (58.8)	106 (52.5) (63.5)	125

	Confirmed (%)	Probabal (%)	Unknown (%)	Non- exposure (%)	Contact (%)
15 yrs or younger	19 (54.3)	39 (45.9)	189 (44.5)	84 (41.6)	46 (23.4)
Unreported	2 (5.7)	17 (20.0)	1 (0.2)	7 (3.5)	—
Total reported	33	68	424	195	197
Completing at least 3 doses	29 (87.9)	63 (92.6)	383 (90.3)	170 (87.2)	178 (90.4)
Completing at least 4 doses	29 (87.9)	56 (82.4)	316 (74.5)	129 (66.2)	157 (79.7)
Completing more than 4 doses	1 (3)	3 (4.4)	8 (1.9)	3 (1.5)	1 (0.5)
Average delay between exposure and reporting (days)	1.5	2.8	2.6	1.8	NA
Reported within 2 days of bite	28 (84.8)	48 (70.6)	324 (76.4)	159 (81.5)	—
Interviewed	35 (100)	82 (96.5)	111 (26.1)	171 (84.7)	—
Reported to peripheral clinic before reporting to the ARMC	0 (0)	6 (7.3)	15 (13.5)	21 (12.3)	—
Reported to a peripheral clinic only (unreported to ARMC)	0 (0)	7 (8.5)	0 (0)	3 (1.8)	—
Reported to any other hospital	0 (0)	13 (15.9)	15 (13.5)	24 (14)	—
Wound location**	Legs	8 (22.9)	31 (37.8)	51 (45.9)	79 (46.2)
Feet	4 (11.4)	15 (18.3)	26	26 (15.2)	—
Arms	9 (25.7)	5 (6.1)	6 (5.4)	14 (8.2)	—

	Confirmed (%)	Probabal (%)	Unknown (%)	Non- exposure (%)	Contact (%)
Hands	8 (22.9)	23 (28)	23	24 (14)	—
				(20.7)	
Upper body	5 (14.3)	4 (4.9)	7 (6.3)	24 (14)	—
Head or neck	2 (5.7)	4 (4.9)	1 (0.9)	6 (3.5)	—
Wound type**					
Skin	21 (60)	57	92 (82.9)	126	
broken		(69.5)		(73.7)	
Superficial	25 (71.4)	59 (72)	94	134 (78.4)	—
				(84.7)	
Deep	2 (5.7)	5 (6.1)	6 (5.4)	10 (5.8)	—
Scratch	8 (22.9)	15 (18.3)	18	32 (18.7)	—
				(16.2)	
Bite	29 (82.9)	64 (78)	91 (82)	144 (84.2)	—
Multiple	1 (2.9)	1 (1.2)	1 (0.9)	3 (1.8)	—
Over clothes	7 (20)	9 (11)	31	45 (26.3)	—
				(27.9)	
Washed wound	28 (80)	62 (75.6)	96	139 (81.3)	—
				(86.5)	

*Bold rows are denominators for subsequent rows. **Categories are not mutually exclusive and were assigned as they applied to each bite victim.

A total of 201 patients reported as contacts with a probable rabies case (human or animal), making up 20% of patients receiving PEP. Fig. 4B shows the distributions of contacts per case, with contacts with the four human cases comprising the majority of these patients (41.6%). One bovine case, for which the contacts were people that consumed the meat of the animal, subsequently tested negative. In addition, details about the nature and timing of the contact, and for a subset details on the probable animal itself (6 unknown cases), were not recorded at the clinic.

Overall, demographics of patients were skewed male (59.1%) and 15 years of age or younger (39.9%), with almost 50% of probable/confirmed rabies exposures 15 years of age or younger compared to

37% of the population in that age group in Moramanga (R. Ratovoson, unpublished data from the Health and Demographic Surveillance System (HDSS) in 3 communes of Moramanga district). For interviewed bite victims ($N = 399$), we also had data on characteristics of the exposure and post-bite response. The majority of wounds were superficial, but with skin broken. Bites to the head or neck and non-superficial bite injuries made up a small fraction of overall exposures (9%), and most wounds were reported to be from bites vs. scratches. Overall, 81.4% of interviewed bite victims reported washing the wound with soap and water (Table 2). 13% of interviewees reported to peripheral clinics before reporting to the ARMC, with 42 of these 52 patients reporting to a peripheral clinic before reporting for PEP at the ARMC and the 10 remaining patients reporting only to a peripheral clinic (i.e. did not report for PEP).

We identified a total of 27 people that did not seek PEP, 19 of which were confirmed or probable rabies exposures, resulting in four human deaths (details in Table 3). The remaining 23 were identified during contact tracing investigations and were in good health at the time of investigation; nine of these people reported for PEP after the investigation (5 probable, 2 confirmed exposures, 2 non-exposures). Of the 17 people that reported a reason for not seeking PEP, most were due to ignorance/misconceptions about rabies ($n = 9$, including thinking the animal was too young to be infected with rabies, not thinking a scratch could result in transmission, reliance on traditional medicine, and complete ignorance of PEP/rabies) and lack of funds to travel to the health center ($n = 8$).

Table 3. Details of the human deaths in the district during the study period.

Case (Age, Sex)	Type of exposure	Biting animal	Health-seeking and wound response	Time between bite and death
Confirmed (3, F)	Superficial scratch to the face	Owned dog, killed after biting	Did not report to the CTAR or any other hospitals; did not wash wound, but applied tambavy (a local plant).	2 months
Suspected (67, M)	Bite, no details on location	Owned dog, disappeared after the bite	No details but did not report for PEP.	1 month
Suspected (61, M)	Superficial bite to the hands	Owned dog, killed after biting	Reported to peripheral clinic and was referred to the CTAR, but did not report for PEP; washed wound and applied oil.	2 months

Case (Age, Sex)	Type of exposure	Biting animal	Health-seeking and wound response	Time between bite and death
Suspected (45, M)	Deep bite to the hands	Unknown dog, disappeared after the bite	Reported to peripheral clinic and was referred to the CTAR, but did not report for PEP; washed wound.	1 year

1.4.4 Deaths averted and current burden of human rabies

We calculated an overall incidence of 189 bites per 100,000 people annually. Given this bite incidence and other parameters (Table 4), we estimate between 19 and 50 deaths averted by PEP and between 4 and 9 human rabies deaths in the Moramanga district annually. Extrapolating to the population of Madagascar, we estimate a current burden of 282–745 human rabies deaths annually, with PEP averting an additional 1499–3958 human rabies deaths. Overall, we estimate a rabies exposure incidence of 42–110 per 100,000 persons annually.

Table 4. Parameters for decision tree model (note that exposures exclude contacts with probable cases).

Parameter	Value	Description
Overall bite incidence per 100,000 people	189	$12 \times$ average of monthly bites (both unreported and reported) between Aug and Dec 2017, when systematic triage was in place
Proportion of overall bites due to rabid animals, prabid	0.22– 0.58	The average monthly proportion of probable/confirmed exposures only (lower limit) or probable/confirmed AND unknown exposures (upper limit) between Aug and Dec 2017, when systematic triage was in place.
Proportion of rabies exposures that seek PEP, prepost	0.84	The proportion of probable/confirmed exposures which reported to the ARMC

Parameter	Value Description
Proportion of rabies exposures that result in infection in the absence of PEP, p_{infect}	0.164 Changalucha et al. 2018 (submitted) [12]
Moramanga population	328,000 Midpoint between World Pop 2015 and 2020 UN adjusted population projections [8]
Madagascar population	26,017 Midpoint between World Pop 2015 and 2020 UN adjusted population projections [8]

1.5 Discussion

1.5.1 Key findings

Our results demonstrate that canine rabies is widespread in the Moramanga District and results in a high incidence of human exposures. Current free provisioning of PEP to patients is estimated to prevent the majority of deaths resulting from these exposures. Furthermore, clinic practice of ID administration of PEP uses half the vaccine volume compared to IM administration and shows how vial sharing practices can be implemented effectively in an endemic setting in sub-Saharan Africa. Despite these successful practices, canine rabies is still responsible for a significant burden of human deaths and drives high demand for PEP. The substantial costs of procuring and providing free PEP are currently borne by IPM, but would otherwise fall to Madagascar's health system and/or patients potentially leading to more human rabies deaths.

While approximately 20% of patients reporting for PEP were classified as rabies exposures, an additional 20% were due to low-to-no risk contacts with confirmed or probable animal and human cases, many of which do not fit the WHO case definition for a rabies exposure [13]. Vaccination of loosely defined exposures has been reported in Bhutan, as well, where PEP is provided at no-cost to patients [15]. These practices may jeopardize vaccination of at-risk persons when PEP availability is limited, as occurred during March 2018 when limited vaccine stocks were used to vaccinate 42 contacts around a human case and subsequently resulted in a stockout at the Moramanga ARMC. Training to ensure that health workers can effectively obtain 5×0.1 mL injections from 0.5 mL vaccine vials would also enable more people to be treated with potential to reduce costs and the risk of vaccine shortages. Rabies control in the dog population would reduce the number of rabies exposures and contacts with

human and animal rabies cases, and could therefore reduce the demand for PEP by over 40%.

Six times as many animal cases were laboratory confirmed during our study period than in the previous 16 months (three animal cases confirmed in the district). Given that between 2011 and 2015, an annual average of 60 rabies case were confirmed in the country, our results suggest significant underreporting of animal rabies both in the Moramanga district and nationally. Through combined clinical and laboratory diagnosis, we were able to determine the rabies status of 40% of biting animals overall and a higher proportion of animals investigated (70%). Clinic-based triage of bite patients doubled the proportion of exposures we were able to classify. While we did not detect many linked animal cases (either source or secondary) through contact tracing as demonstrated previously in Tanzania [16], we identified an additional 19 probable/confirmed exposures, 7 of whom reported to the ARMC after the investigation. In Madagascar, when investigations of suspected human and laboratory confirmed animal cases are conducted leads to the provision of PEP to people who have been in contact with these animals or people. However, shifting effort from these case investigations which focus on vaccinating loosely-defined and likely low-risk contacts, towards routine investigations of probable rabid animal bites to identify untreated exposures, could be a more effective response to prevent human deaths while increasing case detection as part of surveillance [17], [18].

1.5.2 Strengths and limitations

We did not address the potential misclassification of rabies cases through our investigations. Overall, 86% of samples from suspected animals were confirmed positive; however, only 22 samples were tested from the district during this period. Increased efforts to laboratory confirm cases could improve confidence in clinical diagnosis. In general, we believe that our case definition for probable rabies was conservative and likely underestimates the true proportion of rabies exposures (see Section 2, case definitions). Moreover, we may have underestimated rabies exposures and overestimated reporting as investigations were initiated only for patients reporting to the ARMC. We likely missed individuals that reported only to peripheral clinics or that did not report at all (that were not linked to other ARMC patients). Bites by vaccinated dogs also appear to be disproportionately represented in the ARMC as unpublished data from a recent vaccination campaign suggests much lower dog vaccination coverage before the campaign was implemented (5% pre-April 2018, M. Rajeev unpublished data). During our study, only six patients bitten in the Moramanga District reported directly to IPM without referral, the nearest other ARMC, suggesting that most bite victims in the district that seek PEP are captured at the Moramanga ARMC.

We make several further simplifying assumptions in our estimations of rabies burden in the Moramanga District and our extrapolations to Madagascar. We did not incorporate risks due to incomplete

or delayed PEP or for severe exposures that did not receive RIG. Since no deaths were reported from patients who received delayed/incomplete PEP, PEP completion was high, and severe exposures (i.e. deep wounds) uncommon, we believe this will not have introduced major bias. We did not account for vaccine availability and assumed that all patients that reported to the ARMC received PEP. Although the clinic did not experience PEP shortages during our study, in March 2018 the entire country experienced a stockout, with no vaccine available at the Moramanga ARMC for two weeks. We also assumed uniform rabies incidence and reporting across Madagascar. Given that only 31 of 114 districts have an ARMC, this likely underestimates the burden and overestimates deaths averted. Data from other districts on bite incidence, rabies exposures, health seeking behavior, and PEP adherence and availability would improve our estimates and understanding of rabies risk across Madagascar.

1.5.3 Wider context

The animal and patient characteristics described in our study are similar to most other rabies endemic settings, with domestic dogs responsible for the majority of animal bites and rabies cases [19], [20], [21], rabies exposures disproportionately affecting children under 15 years of age [12], [22], patient demographics skewed male [15], [23], [24], and high risk exposures (i.e. deep wounds or bites to the head or neck) generally rare [25]. Unlike in some other rabies endemic countries, the majority of patients reported washing the wound with soap and water, which can greatly reduce risk of transmission [26], [27], [28], [29]. Our estimates of incidence of bite patients, rabies exposures, and human rabies deaths were similar to those from a wide range of endemic settings [19], [21], [22], [29]. This is the first estimate of rabies burden in Madagascar based on data specific to the country and is in line with the previous estimate of burden for Madagascar using data from sub-Saharan Africa [1].

A higher proportion of suspect exposures sought (85%) and completed PEP (90%) compared to other regions with endemic rabies, where PEP is only available at a high cost to patients and a lower proportion of rabies exposed persons receive PEP [21], [22], [24], [30], [31]. Few other studies have described health-seeking behavior and PEP adherence in settings where PEP is free; however, in both Bhutan and Phnom Phen in Cambodia where PEP is provided at no charge to patients, approximately 80–90% receive and complete PEP [15], [32]. Regardless of whether PEP is free, costs to patients (in the case of free PEP, indirect costs) and limited geographical access seem to present the greatest barriers [17], [22], [33]. In addition, awareness on the part of both patients and clinicians responsible for referrals also contribute to bite victims not receiving PEP [34].

We were able to determine the rabies status for animals we investigated to a comparable level as that reported in similar studies in Haiti and Tanzania [20], [35]. Overall, approximately 20% of animal

bites were determined to be likely rabies exposures compared to 13% in Haiti [20], 73% in Ethiopia [21], and 62% in Tanzania [22]. This variation may be due to differences in dog vaccination, as well as higher health seeking of people bitten by non-rabid animals in free settings (higher levels of dog vaccination coverage in Haiti and Tanzania; more costly PEP in Ethiopia and Tanzania). Our results suggest that implementing recently developed integrated bite case management programs which use risk assessments to prioritize PEP administration [17], [34], [36] and using bite patients as sentinels for rabies surveillance [35] are feasible and effective options to better manage PEP and improve surveillance in Madagascar, especially as control in the dog population is implemented.

1.5.4 Conclusions & recommendations

Our findings show that canine rabies is responsible for a high incidence of human rabies exposures and preventable rabies deaths in Madagascar, and accounts for a large proportion of the demand for PEP. Given current successful ID administration of PEP and vial sharing practices, adoption of the latest WHO recommendations for PEP administration using the abridged 1-week ID regimen could be implemented immediately in Madagascar to reduce PEP costs. Shifting away from control strategies of reactive culling to mass dog vaccination would further reduce both the high costs of PEP and the burden of human rabies. Increasing access to PEP and awareness for its need could also greatly reduce the burden of human rabies, especially given its limited availability within Madagascar. Nonetheless, the fact that where PEP is available, it is provided to patients for free, appears to result in relatively high health seeking and adherence in comparison to other low-income settings. In general, more judicious use of PEP may be warranted as access is expanded and vaccine use increases. Particularly, if mass dog vaccination is implemented and risk of rabies exposures decrease, integrated bite case management [36] could be used to further reduce PEP demand while enhancing surveillance of animal cases and identification of exposed persons [20], [35]. However, this would require improved integration of activities and coordination between the health and veterinary sectors. Given the push to eliminate deaths due to human rabies [4], our results demonstrate that investing in rabies control as a public good through providing free PEP can prevent needless human deaths, and in combination with mass dog vaccination has the potential to greatly reduce and eventually eliminate rabies from Madagascar.

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1.7 Conflict of interest statement

The authors declare no conflicts of interest.

1.8 Author contributions

MR, GE, CH, SF, HG, JMH, MA, CJEM, and KH conceived and designed the study. MR, GE, CH, SF, HG, JMH, RR, RR, LR, LB acquired and/or analyzed the data. MR, CJEM, and KH drafted the article. All authors provided critical feedback and approved the final version to be submitted.

1.9 Data availability

Anonymized data are available on request and pending approval of the Ministry of Public Health and IPM.

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Chapter 2

How geographic access to care shapes disease burden: the current impact of post-exposure prophylaxis and potential for expanded access to prevent human rabies deaths in Madagascar

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2.1 Abstract

2.1.1 Background

Post-exposure prophylaxis (PEP) is highly effective at preventing human rabies deaths, however access to PEP is limited in many rabies endemic countries. The 2018 decision by Gavi to add human rabies vaccine to its investment portfolio should expand PEP availability and reduce rabies deaths. We explore how geographic access to PEP impacts the rabies burden in Madagascar and the potential benefits of improved provisioning.

2.1.2 Methodology & Principal Findings

We use spatially resolved data on numbers of bite patients seeking PEP across Madagascar and estimates of travel times to the closest clinic providing PEP ($N = 31$) in a Bayesian regression framework to estimate how geographic access predicts reported bite incidence. We find that travel times strongly predict reported bite incidence across the country. Using resulting estimates in an adapted decision tree, we extrapolate rabies deaths and reporting and find that geographic access to PEP shapes burden sub-nationally. We estimate 960 human rabies deaths annually (95% Prediction Intervals (PI): 790 - 1120), with PEP averting an additional 800 deaths (95% PI: 800 (95% PI: 640 - 970) each year. Under these assumptions, we find that expanding PEP to one clinic per district (83 additional clinics) could reduce deaths by 19%, but even with all major primary clinics provisioning PEP (1733 additional clinics), we still expect substantial rabies mortality. Our quantitative estimates are most sensitive to assumptions of underlying rabies exposure incidence, but qualitative patterns of the impacts of travel times and expanded PEP access are robust.

2.1.3 Conclusions & Significance

PEP is effective at preventing rabies deaths, and in the absence of strong surveillance, targeting underserved populations may be the most equitable way to provision PEP. Given the potential for countries to use Gavi funding to expand access to PEP in the coming years, this framework could be used as a first step to guide expansion and improve targeting of interventions in similar endemic settings where PEP access is geographically restricted and baseline data on rabies risk is lacking. While better PEP access should save many lives, improved outreach, surveillance, and dog vaccination will be necessary, and if rolled out with Gavi investment, could catalyze progress towards achieving zero rabies deaths.

2.2 Author Summary

Canine rabies causes an estimated 60,000 deaths each year across the world, primarily in low- and middle-income countries where people have limited access to both human vaccines (post-exposure prophylaxis or PEP) and dog rabies vaccines. Given that we have the tools to prevent rabies deaths, a global target has been set to eliminate deaths due to canine rabies by 2030, and recently, Gavi, a multilateral organization that aims to improve access to vaccines in the poorest countries, added human rabies vaccine to its portfolio. In this study, we estimated reported incidence of patients seeking PEP in relation to travel times to clinics provisioning PEP and extrapolate human rabies deaths in Madagascar. We find that PEP currently averts around 800 deaths each year, but that the burden remains high (1000 deaths/ year), particularly in remote, hard-to-reach areas. We show that expanding PEP availability to more clinics could significantly reduce rabies deaths in Madagascar, but our results reaffirm that expansion alone is will not achieve the global goal of zero human deaths from dog-mediated rabies by 2030. Combining PEP expansion with outreach, surveillance, and mass dog vaccination programs will be necessary to move Madagascar, and other Low- and Middle-Income countries, forward on the path to rabies elimination.

2.3 Introduction

Inequities in access to care are a major driver of disease burden globally [1]. Often, the populations at greatest risk of a given disease are the most underserved [2]. Delivering interventions to these groups is challenging due to financial and infrastructural limitations and requires careful consideration of how best to allocate limited resources [3].

Canine rabies is estimated to cause approximately 60,000 human deaths annually [4]. Mass vaccination of domestic dogs has been demonstrated to be a highly effective way to control the disease in both animals and humans. While dog vaccination can interrupt transmission in the reservoir, human deaths can also be prevented through prompt administration of post-exposure prophylactic vaccines (PEP) following a bite by a rabid animal [5]. However, access to the human rabies vaccine is limited in many countries where canine rabies is endemic [6–8], and within countries these deaths are often concentrated in rural, underserved communities [9].

In 2015, a global framework to eliminate deaths due to canine rabies by 2030 ('Zero by 30') through a combination of PEP provisioning and dog vaccination was established by the World Health Organization (WHO) and partners [10]. Furthermore, in 2018, Gavi, the Vaccine Alliance, added human rabies vaccines to their proposed investment portfolio [11]. From 2021, Gavi-eligible countries should

be able to apply for support to expand access to these vaccines, with potential to greatly reduce deaths due to rabies.

A primary challenge in expanding access effectively is the lack of data on rabies exposures and deaths in humans and incidence in animals in most rabies-endemic countries [12]. Deaths due to rabies are often severely underreported, with many people dying outside of the health system, often in remote and marginalized communities [13]. Instead of directly measuring rabies deaths, the majority of rabies burden studies use bite patient data on reported bites at clinics provisioning PEP and a decision tree framework to extrapolate deaths, assuming that overall reported bite incidence (i.e. both bites due to non-rabid and rabid animals) is proportional to rabies incidence (i.e. the more bites reported in a location, the higher the incidence of rabies exposures), and that reporting to clinics for PEP is uniform across space [8,14,15]. If applied subnationally, these assumptions would likely underestimate rabies deaths in places with poor access to PEP and may overestimate rabies deaths in places with better access to PEP.

In Madagascar, the Institut Pasteur de Madagascar (IPM) provides PEP to 30 Ministry of Health clinics, in addition to its own vaccine clinic, where PEP is available at no direct cost to patients [15]. Other than at these 31 clinics, PEP is not available at any other public clinics or through the private sector. In addition, there is limited control of rabies in dog populations and the disease is endemic throughout the country [16,17]. Due to the spatially restricted nature of PEP provisioning and lack of direct costs for PEP, geographic access is likely to be a major driver of disease burden within the country. Previously, we estimated the burden of rabies in Madagascar nationally using data from a single district to extrapolate to the country, but did not account for spatial variation in access [15]. Here, we provide revised estimates of human rabies deaths by incorporating the impact of access to PEP at the sub-national level on preventing human rabies deaths and explore the potential impact of expanding provisioning of human rabies vaccines on further reducing these deaths. This framework may usefully apply to other countries where PEP availability is currently geographically restricted in considering how to most effectively and equitably provision these life-saving vaccines.

2.4 Methods

2.4.1 Estimating geographic access to PEP

To estimate mean and population weighted travel times to the nearest clinic, we used two raster datasets: 1) the friction surface from the Malaria Atlas Project [18] at an $\sim 1 \text{ km}^2$ scale (Fig S1.1A) and 2) the population estimates from the 2015 UN adjusted population projections from World Pop ([19], originally at an $\sim 100\text{m}^2$ resolution, Fig S1.1B), which we aggregated to the friction surface.

From GPS locations of the 31 clinics that currently provision PEP, we estimated the travel time to the nearest clinic at an approximately 1 x 1 km scale as described in [18]. We then extracted the mean and population-weighted mean travel times for each district (2nd level administrative division, N = 114) and commune (the administrative unit below the district, N = 1579), and Euclidean distance, i.e. the minimum distance from the administrative unit centroid to any clinic. We used shapefiles from the UN Office for the Coordination of Humanitarian Affairs for the district and communes boundaries (as of October 31, 2018). To see which metric best predicted ground-truthed travel time data, we compared travel times and distance estimates to driving times collected by IPM during field missions, i.e. time it took to travel by car between two locations excluding break times (N = `rnrow(ttime_driving)`), and patient reported travel times from a subset of Moramanga clinic bite patients (N = 1057), see Fig S1.2 for raw data) by seeing which worked best to predict estimated travel times in a linear model.

2.4.2 Estimating bite incidence

We used two datasets on bite patients reporting to clinics for PEP:

- 1) A national database of individual bite patient forms from the 31 clinics provisioning PEP across the country between 2014 - 2017. These forms were submitted to IPM with frequencies ranging from monthly to annually, included the patient reporting date and were resolved to the district level (patient residence).
- 2) 33 months of data (between October 2016 and June 2019) on patients reporting to the Moramanga clinic resolved to the commune level.

For the national data, some clinics did not submit any data, or had substantial periods (months to a whole year), with no submitted data. To correct for this, we exclude periods of 15 consecutive days with zero submitted records (see Supplementary Appendix, section S2). For each clinic we divided the total number of bites reported in a given year by the estimated proportion of forms which were not submitted (under-submission). Due to yearly variation in submissions, we took the average of annual bite incidence estimates aggregated to district level. We validated this approach by comparing estimated vial demand given the total reported bites corrected for under-submission to vials provisioned to clinics for 2014-2017 (see Supplementary Appendix, section S2). At both the commune and district administrative level, we assigned clinic catchments by determining which were closest in terms of travel times for the majority of the population within the administrative unit. For national data, we excluded any districts in a catchment of a clinic which submitted less than 10 forms and any years for which we estimated less than 25% of forms were submitted.

2.4.3 Modeling reported bite incidence as a function of access

We modeled the number of reported bites as a function of travel time (T) using a Poisson regression:

$$\mu_i = e^{(\beta_t T_i + \beta_0)} P_i$$

$$y_i = Poisson(\mu_i)$$

where y_i is the average number of bites reported to a clinic annually and μ_i the expected number of bite patients presenting at the clinic as a function of travel time (T_i) and human population size (P_i) (an offset which scales the incidence to the expected number of bites) for a given source location (district or commune). We fit this model to both the national data (district level) and the Moramanga data (commune level). To more directly compare estimates between datasets, we also modeled the national data with a latent commune-level travel time covariate (T_j):

$$\mu_i = \sum_{j=1}^J e^{(\beta_t T_j + \beta_{0j})} P_j$$

As travel times are correlated with population size (Fig S3.1), we also compared how well bites were predicted by population size alone, and in combination with travel times. For the models with population size, we removed the offset and used either population size alone ($\mu_i = e^{(\beta_p P_i + \beta_0)}$) or population size and travel times ($\mu_i = e^{(\beta_t T_i + \beta_p P_i + \beta_0)}$) as predictors.

For the models fit to the national data, we also modeled variation between clinics with a catchment random effect: $B_{0,k} \sim norm(\mu, \sigma_0)$, where μ is the mean and σ_0 is standard deviation and $B_{0,k}$ is the catchment level intercept.

We tested whether the catchment random effect captured overdispersion in the data (i.e. variance > mean – the expectation given a Poisson distribution) rather than any catchment specific effects by extending these models with an overdispersion parameter: $\epsilon_i \sim norm(0, \sigma_e)$, where σ_e is the standard deviation around a random variable with mean of zero [20]:

$$\mu_i = e^{(\sum_{j=1}^J \beta_j X_j + \epsilon_i)} P_i$$

where $\sum_{j=1}^J \beta_j X_j$ is the sum of the all parameters for a given model. We fit all models in a Bayesian regression framework via MCMC using the R package ‘rjags’ [21]. We used model estimates to

generate fitted and out-of-fit predictions, and examined the sensitivity of estimates to adjustments for under-submission of forms (Supplementary Appendix, section S3).

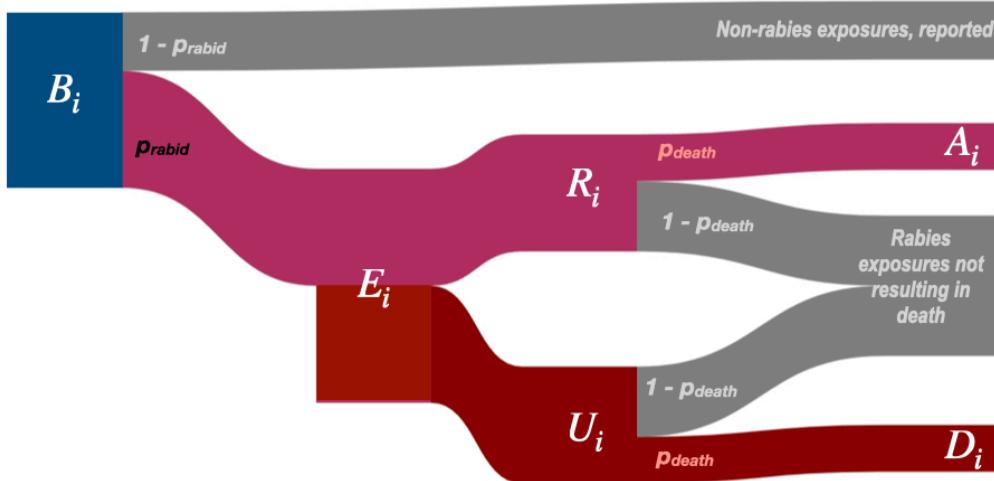
2.4.4 Modeling human rabies deaths

We estimate rabies deaths as a function of the number of bites predicted by our model and estimates of endemic rabies exposure incidence using an adapted decision tree framework. Table 1 lists all parameter values and their sources. Fig 1 describes how these parameters are used in the decision tree and the key outputs (A_i , deaths averted by PEP, and D_i , deaths due to rabies).

Table 1. Parameters used in the decision tree to estimate human rabies deaths at the administrative level.

Parameter	Value	Description	Source
B_i	Function of travel time to closest clinic provisioning PEP	Modeled estimates of reported bite incidence	Bayesian regression model (see Methods)
E_i	Triangular($a = 15$, $b = 76$, $c = 42$)	Annual exposures per 100,000 persons	[4,15], see Fig S4.1
p_{rabid}	Triangular($a = 0.2$, $b = 0.6$, $c = 0.4$)	Proportion of reported bites that are rabies exposures ¹	[15]
ρ_{max}	0.98	The maximum reporting possible for any location; data from the commune closest to the Moramanga PEP clinic (average of 3.12 minutes travel time to the clinic)	[15]
p_{death}	0.16	The probability of death given a rabies exposure	

• ¹ p_{rabid} is constrained so that rabid reported bites cannot exceed the total expected number of rabies exposures (E_i) or maximum reporting in a given simulation (ρ_{max}).



2.4.4.1 Fig 1. Decision tree for burden estimation.

For a given administrative unit i , human deaths due to rabies (D_i) are calculated from model predicted reported bites (B_i). To get R_i , the number of reported bites that were rabies exposures, we multiply B_i by p_{rabid} , the proportion of reported bites that are rabies exposures. R_i is subtracted from E_i to get the number of unreported bites (U_i) and then multiplied by the probability of death given a rabies exposure (p_{death}) to get deaths due to rabies (D_i). Similarly, deaths averted by PEP, A_i , are estimated by multiplying R_i by p_{death} , i.e. those who would have died given exposure, but instead received PEP. Both E_i and p_{rabid} are drawn from a triangular distribution. Parameter values and sources are in Table 1.

For E_i , we center the distribution at the lower end of our estimated exposure incidence from the Moramanga District (42 exposures/100,000 persons), with a range applied assuming 1% rabies incidence in dogs (estimated across a range of human-to-dog ratios between 5 - 25) and that on average a rabid dog exposes 0.39 persons [4] (see Fig S4.1). As there is little data on dog population size and human exposure incidence in Madagascar[16,23], the range we used encompasses both observed human-to-dog ratios across Africa [14,24] and recent subnational estimates from Madagascar [25], and generates similar exposure incidences as observed previously across Africa [26,27]. Given previously high observed compliance in Madagascar [15], we assume that all rabies exposed patients who report to a clinic receive and complete PEP, and PEP is completely effective at preventing rabies.

2.4.5 Estimating the impact of expanding PEP provisioning

We developed a framework to rank clinics by how much their PEP provision improves access for underserved communities, estimating incremental reductions in burden and increases in vaccine de-

mand. Specifically, we aggregated our model-predicted estimates of annual bites to the clinic level. As multiple clinics may serve a single district or commune, we allocated bites to clinics according to the proportion of the population in each administrative unit which were closest. For each clinic, we simulate throughput by randomly assigning patient presentation dates, and then assume perfect compliance (i.e. patients report for all doses) to generate subsequent vaccination dates. We use these dates to estimate vial usage given routine vial sharing practices in Madagascar [15], but assuming adoption of the WHO-recommended abridged intradermal regimen (2 x 0.1 ml injections on days 0, 3, and 7 [28]). For both burden and vial estimates, we take the mean of 1000 simulations as each clinic is added.

We simulate expansion first to each district ($N = 114$) and then to each commune in the country for all communes with a clinic. We select the primary clinic (primary health facility, usually with capacity to provision vaccines) in the highest density grid cell of the administrative unit as candidates for expansion. For the 85 communes without a primary clinic, we chose the secondary clinic (secondary health facility, often without formal vaccination capacity) in the highest density grid cell. 94 communes lacked any health facilities. Finally, we explore a scenario where all additional primary clinics (totaling 1733) provision PEP.

We tested three metrics for ranking additional clinics: 1) The proportion of people living >3 hours from a existing PEP clinic that provisions PEP for which travel times were reduced; 2) This proportion (1), weighted by the magnitude of the change in travel times and 3) The mean reduction in travel times for people living >3 hours from an existing PEP clinic. We simulated expansion of clinics provisioning PEP to each district using these three metrics and chose the metric which decreased burden the most compared to simulations ($N = 10$) where clinics were added randomly to districts for the full expansion of PEP. For the full simulation of expanded access, once clinics reduced travel times for less than 0.01% of the population (< 2400 living greater than x hrs away, starting with $x = 3$ hrs), we reduced the travel time threshold by 25%.

2.4.6 Sensitivity analysis

To test the effect of our model assumptions on estimates of rabies burden and vial demand, we did a univariate sensitivity analysis of both parameters from the models of bite incidence and the decision tree (see Table S6.1 & S6.2 for parameter ranges used). We also examined how systematic variation in rabies incidence with human population size affected burden estimates. Specifically, if human-to-dog ratios are positively correlated with human populations (i.e. dog ownership/populations are higher in more populated, urban areas), we might expect higher rabies exposure incidence as population size increases. Alternatively, if human-to-dog ratios inversely correlate with population size (i.e. dog

ownership is more common in less populated, rural areas), we might expect exposure incidence to scale negatively with population size. We use scaling factors to scale incidence either positively or negatively with observed population sizes at the district and commune levels, while constraining them to the range of exposure incidence used in the main analyses (15.6 - 76 exposures per 100,000 persons, Fig S4.2) and simulated baseline burden, as well as expanded PEP access.

2.4.7 Data and analyses

All analyses were done in R version 4.0.2 (2020-06-22) [29] and using the packages listed in the supplementary references (Supplementary appendix, section S7). All processed data, code, and outputs are archived on Zenodo (<http://doi.org/10.5281/zenodo.4064312> and <https://doi.org/10.5281/zenodo.4064304>), and maintained at <https://github.com/mrajeev08/MadaAccess>. The raw bite patient data at the national level are maintained in two secure REDCap (project-redcap.org) databases, one for IPM and another for all peripheral clinics provisioning PEP. These databases were last queried on September 19, 2019 for these analyses. The IPM GIS unit provided the data on geolocated clinics across the country. Anonymized raw bite patient data and full data on geolocated clinics are available from IPM following institutional data transfer protocols. Anonymized raw data collected from the Moramanga District were retrieved from the Wise Monkey Portal (wisemonkeyfoundation.org) on the same date and are shared in the archived repository.

2.4.8 Ethics statement

Data collection from the Moramanga District was approved by the Princeton University IRB (7801) and the Madagascar Ministry of Public Health Ethics Committee (105-MSANP/CE). Oral informed consent was obtained from all interviewed participants. Data collected from bite patients at the national level are maintained jointly by the Ministry of Health and IPM as a routine part of PEP provisioning.

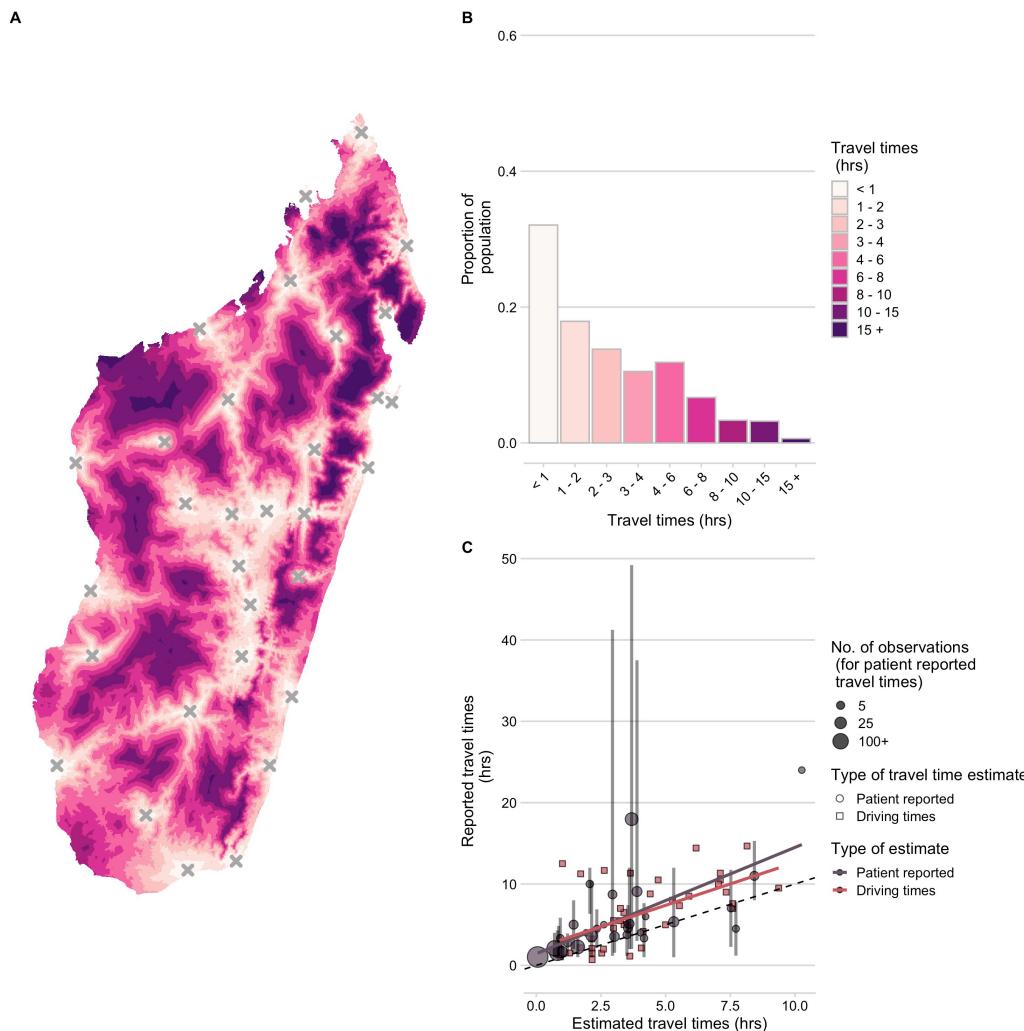
2.5 Results

2.5.1 Estimates of travel times to clinics are high and variable across Madagascar.

Based on the estimates from the friction surface, approximately 36% of the population of Madagascar are estimated to live over 3 hours from a clinic (Fig 2). However, we found that these estimates

underestimated both driving times across the country and patient-reported travel times to the Moramanga PEP clinic (Fig 2C). Patient reported travel times were highly variable for a given commune compared to the estimated travel times (Fig S1.2), potentially due to the fact that the friction surface assumes that the fastest available mode of transport is used across each grid cell (i.e. the presence of a road indicates that all travel through that grid cell is by vehicle). However, patients reported using multiple modes of transport, with some individuals walking days to the Moramanga PEP clinic (Fig S1.3).

While the travel time estimates may not reflect exact distributions of travel times, they were correlated with ground-truthed driving and patient-reported times and likely reflect patterns of access over the country (Fig 3C, Fig S1.4). Travel times weighted by population at the grid cell level were a better predictor than unweighted travel times or distance ($R^2 = 0.43$, Table S1.1), therefore, we use population-weighted travel time as a proxy for access at the commune/district level in subsequent analyses.

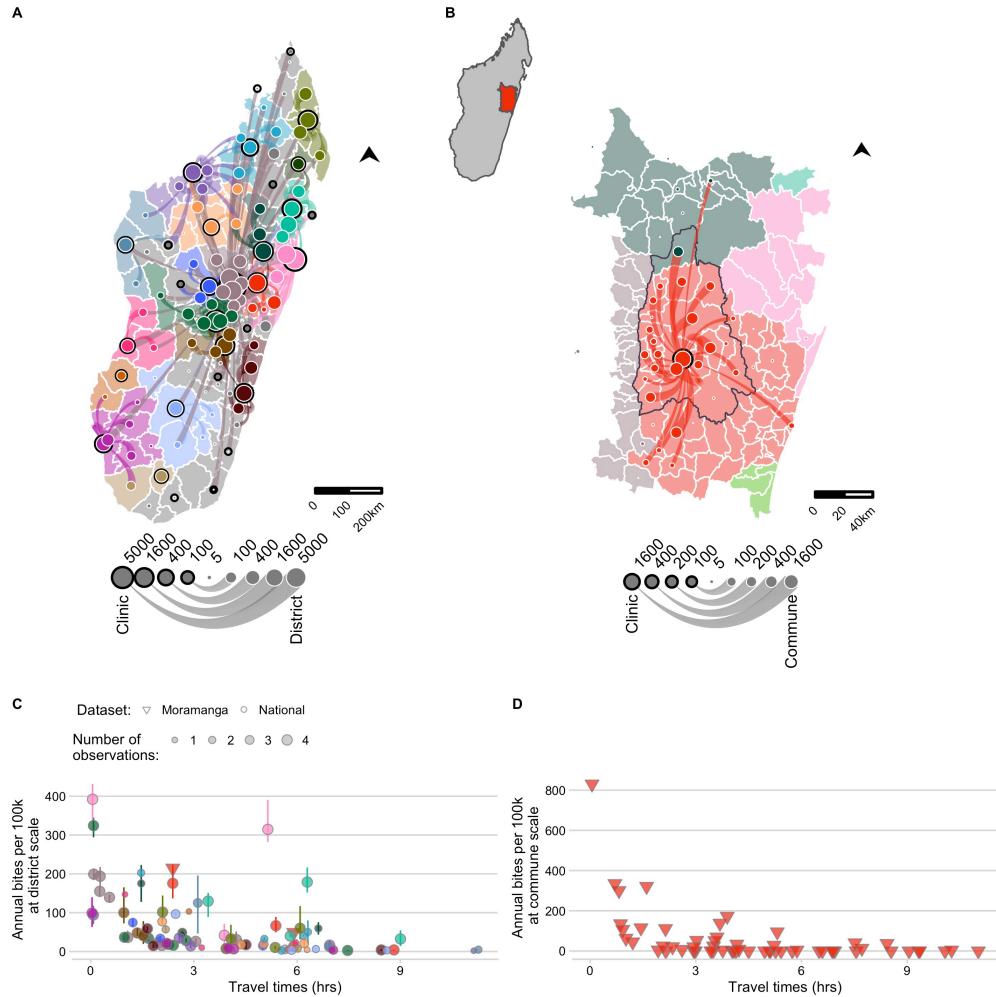


2.5.1.1 Fig 2. Travel times to clinics provisioning PEP across Madagascar.

(A) Estimated at an $\sim 1 \text{ km}^2$ scale. (B) Distribution of the population across travel times. (C) Correlation between ground-truthed travel times (mean of patient reported travel times to the Moramanga PEP clinic at the commune level and reported driving times between GPS points) and friction surface travel time estimates. The vertical lines show the 95% quantiles for reported travel times and the point size shows the number of observations for each commune. The best fit lines (red and grey) from a linear model where observed travel times are predicted by estimated travel times for each data source are also shown. The dashed black line is the 1:1 line.

2.5.2 As travel times increase, reported bite incidence decreases.

Bite incidence estimates generally increased with decreasing weighted travel times at both administrative scales (district and commune), although there was considerable variation between catchments for the magnitude of this relationship (Fig 3C and D). After additionally excluding any year with less than 25% of forms submitted, our final dataset consisted of estimates of average bite incidence for 83 of 114 districts (Fig 3C), and 58 communes within the catchment of the Moramanga District (Fig 3D, see Supplementary Appendix section S2 for more details). For the national data, there were two outliers, Toamasina II (the sub-urban district surrounding the city of Toamasina) and Soanierana Ivongo, with higher bite incidence when compared to other districts with similar travel times. While the estimates from the Moramanga data showed higher reported incidence at low travel times at the commune level compared to the district estimates, when aggregated to the district, bite incidence estimates fell within the ranges observed from the national dataset.

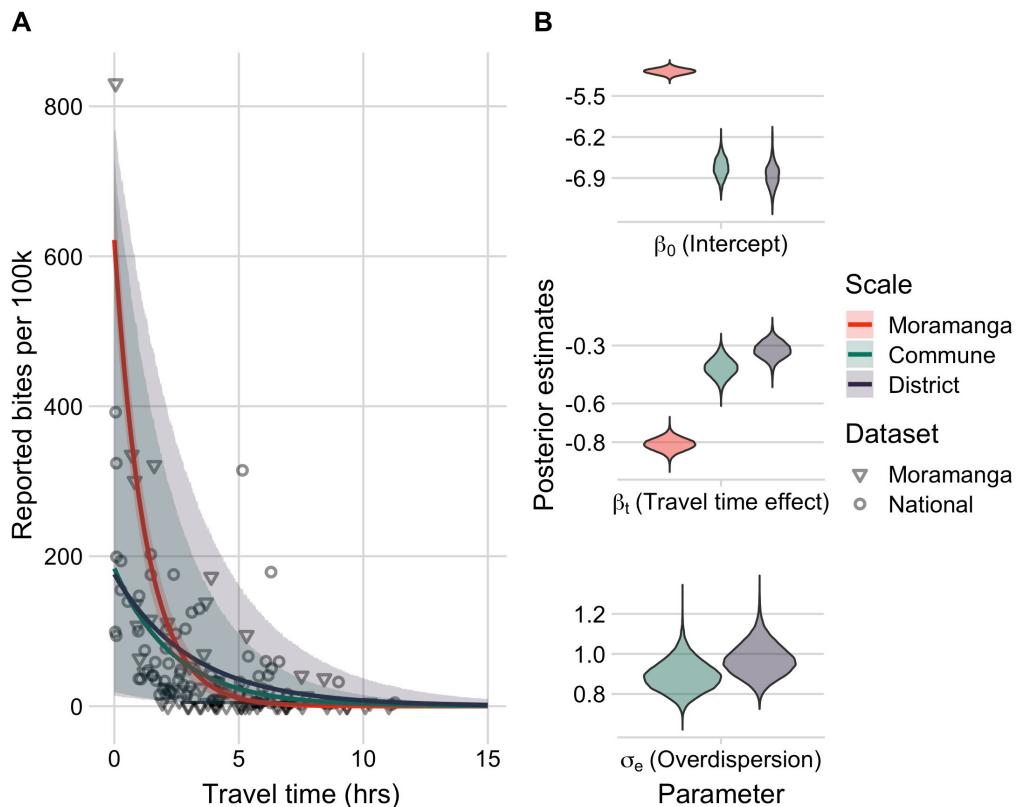


2.5.2.1 Fig 3. The network of patient presentations and estimates of annual bite incidence.

(A) at the district level for the national data and (B) commune level for the Moramanga data: circles with a black outline represent the total number of patients reporting to each clinic for which we have data. Color corresponds to the clinic catchment. Circles with a white outline are the total number of bites reported for that administrative unit (plotted as the centroid). Lines show which clinic those patients reported to, with the line width proportional to number of patients from that district reporting to the clinic; flows of less than 5 patients were excluded. Out-of-catchment reporting is indicated where points and line colors are mismatched. For panel (A) districts in catchments excluded due to lack of forms submitted by the clinic are colored in grey. For (B) the inset of Madagascar shows the location of the enlarged area plotted, which shows the district of Moramanga (outlined in black), all communes included in its catchment (red polygons), and other communes where bites were reported to colored by their catchment (C) The estimated average annual bite incidence from the national and Moramanga

data plotted at the district scale (both datasets) and at the (D) commune scale (Moramanga dataset). Colors correspond to the clinic catchment, shape indicates the dataset, and the size of the point indicates the number of observations (i.e. the number of years for which data was available for the national data; note for Moramanga 33 months of data were used). The point lines indicate the range of estimated bite incidence for each district.

Our modeling results show that travel times were a strong and consistent predictor of reported bite incidence in both datasets and across scales with the best fitting models including travel times and an overdispersion parameter (Fig 4, see Supplementary Appendix section S3 for comparisons to models with catchment effects and with population size as a covariate). As the predictions of the model fit to the Moramanga data without accounting for overdispersion fall within the prediction intervals for the models fit to the national data (Fig 4A), for subsequent predictions, we used the parameter estimates from models fit to the national data, which encompass the range of travel time effects observed in our datasets. Moreover, our out-of-fit predictions to the data across scales suggest that the commune model is able to capture travel time impacts at the commune level (Fig S3.3), therefore we use both the district and commune model to disaggregate burden to the finest scale possible. Finally, we examined the sensitivity of models to how we corrected for underreporting of data and found that parameter estimates of travel time impacts were similar across models and performed similarly in prediction (Fig S3.8 and Fig S3.9).



2.5.2.2 Fig 4. Travel times as a predictor of reported bite incidence per 100,000 persons.

(A) The estimated relationship between travel time in hours (*x*-axis) and mean annual reported bite incidence (*y*-axis). The lines are the mean estimates and the envelopes are the 95% prediction intervals generated by drawing 1000 independent samples from the parameter posterior distributions for three candidate models: model with travel times at the 1) commune- and 2) district-level fitted to the national data with an overdispersion parameter (σ_e) and 3) travel times at the commune level fitted to the Moramanga data with a fixed intercept and unadjusted for overdispersion. The points show the data: National data (circles) at the district level used to fit the District and Commune models, and Moramanga data (triangles) at the commune level used to fit the Moramanga model. (B) The posterior distribution of parameters from the respective models for the model intercept, travel time effect, and for overdispersion (national data only).

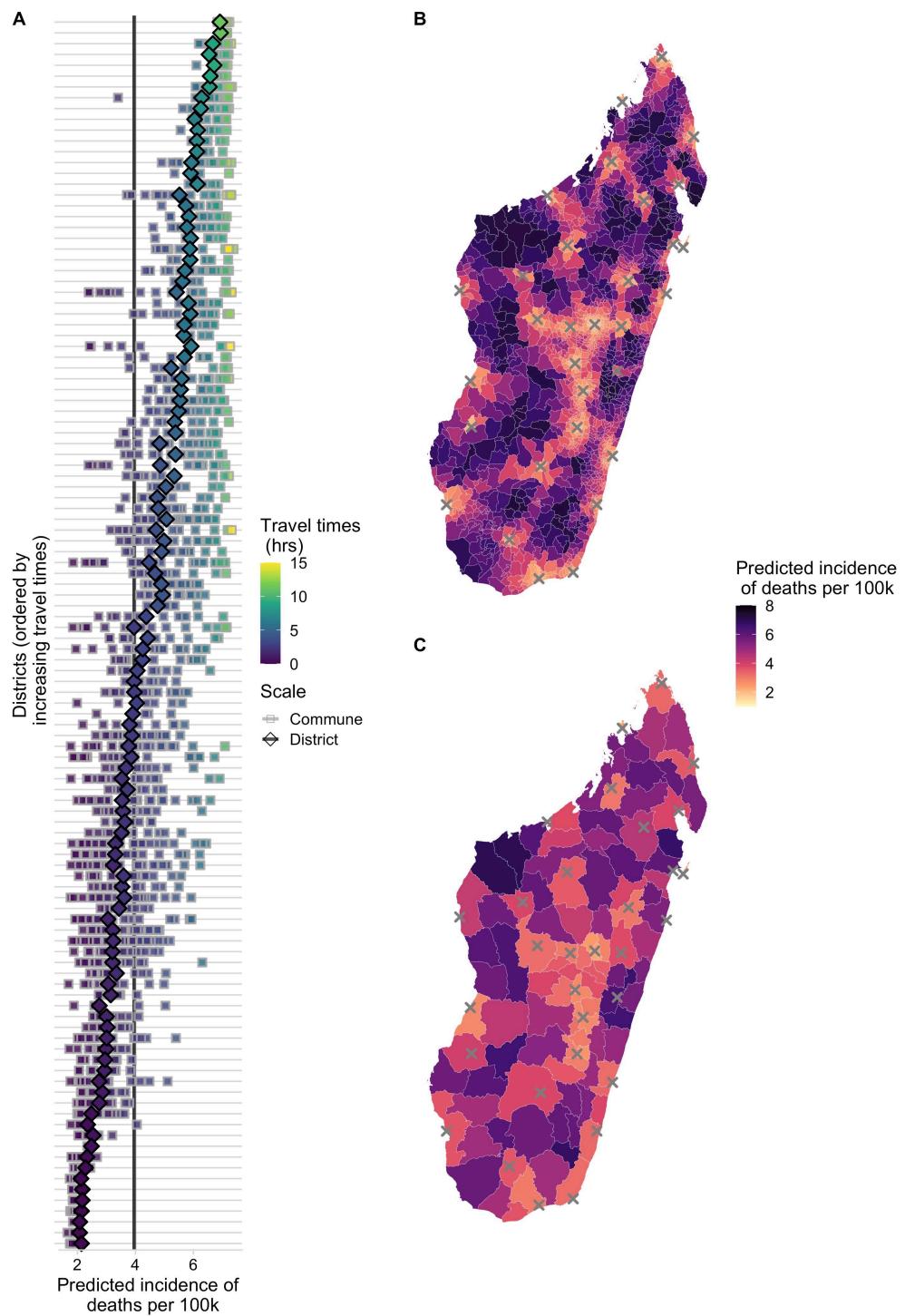
2.5.3 Current provisioning of PEP substantially reduces human rabies deaths, but incidence of deaths remains high in areas with poor access

In general, the incidence of rabies deaths increases with travel times to clinics, and there is significant sub-national variation when deaths are modeled at the district and commune scale, with the least accessible communities having most deaths (Fig 5B & C). We estimate that under the current system of 31 clinics in Madagascar provisioning PEP that approximately 800 (95% PI: 600 - 1000) deaths due to rabies are prevented through PEP each year. Overall, we estimate close to 1000 rabies deaths (95% PI: 800 - 1100) annually in Madagascar. Our estimates vary only slightly depending on the scale of the model (Table 2), but disaggregating deaths to the commune level shows considerable variation in predicted burden within districts (Fig 5A).

2.5.3.1 Table 2. Model predictions of average annual reported bite incidence, total deaths, and deaths averted at the national level for the two models (commune level and district level models with travel time predictor and an overdispersion parameter); 95% prediction interval in parentheses.

Model	Reported bite incidence per 100k	Burden of deaths	Deaths averted by current PEP provisioning
Commune 85 (56 - 129)		963 (795 - 1118)	801 (644 - 968)

Model	Reported bite incidence per 100k	Burden of deaths	Deaths averted by current PEP provisioning
District	85 (52 - 136)	958 (752 - 1156)	807 (609 - 1005)



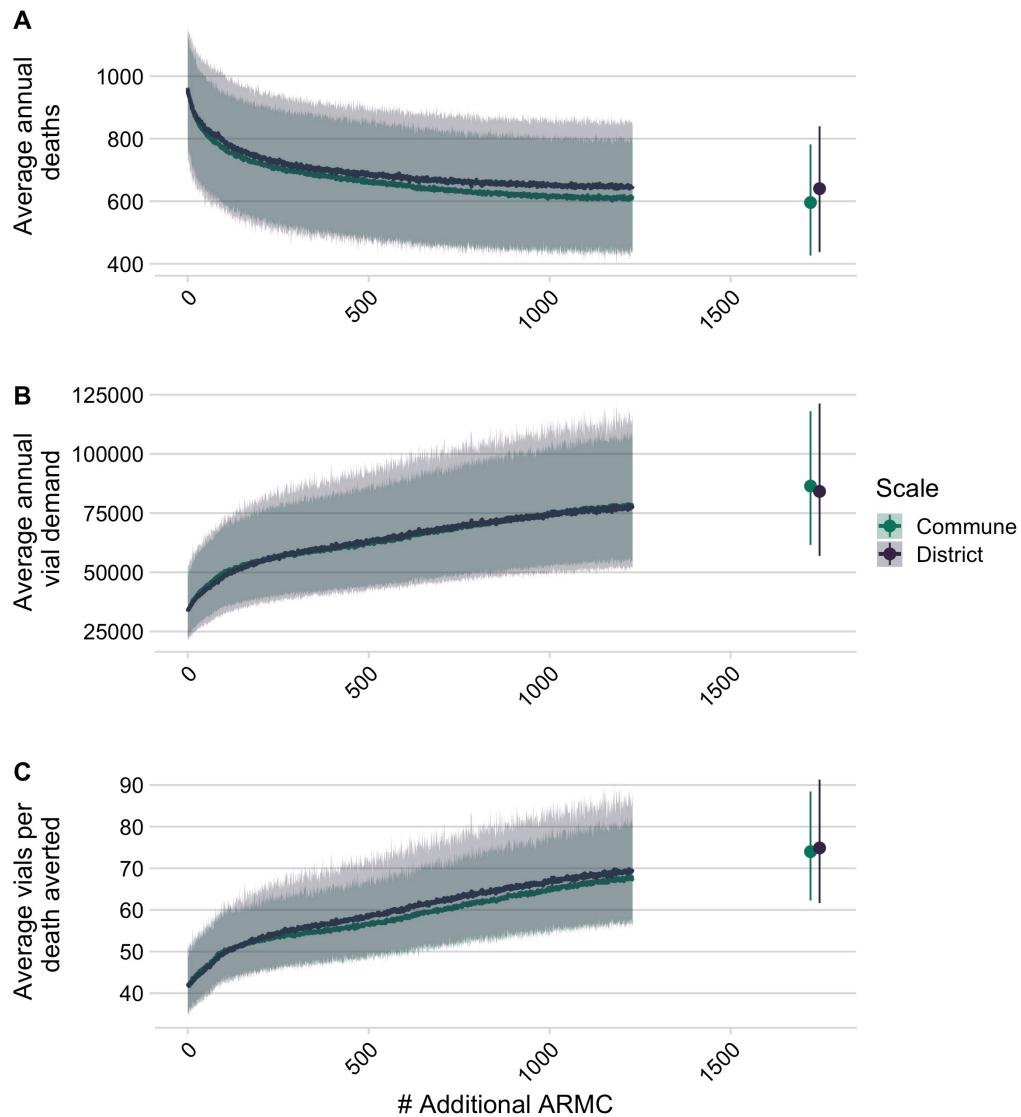
2.5.3.2 Fig 5. Spatial variation in predicted incidence of human rabies deaths per 100,000 persons.

(A) for each district (y-axis) in Madagascar. Diamonds show the predicted incidence for the district model and squares show predicted incidence for the commune model fit to the National data for all communes in a district. Points are colored and districts ordered by travel times. The vertical lines show the average national incidence of human rabies deaths for the commune (grey) and district (black) models. Incidence mapped to the (B) commune- and (C) district-level from the respective models; grey X's show locations of current clinics provisioning PEP

2.5.4 Expanding PEP access to underserved populations is effective at reducing human rabies deaths, but this effect saturates as more clinics provision PEP

We found that targeted expansion of PEP to clinics based on the proportion of the population they reduced travel times for resulted in fewest deaths (Fig S5.1). Here we report results from the commune model, as estimates were consistent across models (Fig 6 and Supplementary appendix, section S5). We estimated that strategic PEP expansion to these additional 83 clinics (1 per district) reduced rabies deaths by 19% (95% PI: 14 - 23%) (Fig 6A). With one clinic per commune (where available, N = 1696), we see a further reduction of 38% (95% PI: 30 - 46%). However, reductions in burden saturate as more clinics are added (Fig S5.2). Even when all primary clinics provision PEP, our model still predicts 600 (95% PI: 400 - 800) deaths per annum, and average reporting of rabies exposures remains approximately 66% (95% PI: 33 - 78%) (Fig S5.5); as more clinics are added, reported bite incidence saturates (Fig S5.4), and patients shift which clinic they report to (S5.7 & S5.8).

Vial demand also outpaces reductions in burden (Fig 6B), with more vials needed per death averted (Fig 6C). Our model predicts an increase from 33500 vials (95% PI: 22900 - 49400) per annum under current provisioning but with the abridged intradermal regimen (i.e. visits on days 0, 3, 7), to ~56900 vials (95% PI: 40200 - 77800) with 250 clinics providing PEP, and ~86400 vials (95% PI: 61600 - 118000) if all primary clinics provision PEP. In these scenarios, clinic catchment populations and throughput decrease, with clinics seeing fewer patients per day (S5.6).



2.5.4.1 *Fig 6. Impact of expanded PEP access on deaths, deaths averted and vial demand.*

(A) Decrease in deaths due to rabies, (B) increase in total # of vials as additional clinics provisioning PEP are added at the national level, and (C) increase in vials needed per death averted based on the two models of reported bites. Lines are the mean of 1000 simulations with envelopes representing 95% prediction intervals. The points show when all additional primary clinics and secondary clinics ($N = 1733$) clinics have been added).

2.5.5 Burden estimates are most sensitive to assumptions of underlying rabies incidence.

While qualitative patterns of the current impact of geographic access on human rabies deaths and the impact of expanding access to PEP on reducing these deaths is robust across a wide range of parameter estimates, our sensitivity analyses show that assumptions of the underlying rabies exposure incidence (E_i) contribute the most uncertainty to our quantitative estimates (Fig S6.1 & 2). Uncertainty in bite model parameters contribute less to uncertainty in estimates of burden or impacts of expanded access. For the estimates of vial demand, uncertainty around the model intercept (i.e. the baseline reported bite incidence) has most impact, rather than the travel time effect or the overdispersion parameter (Fig S6.3). Finally, scaling of incidence with population size (Fig S4.2) modulates the impact of travel times on deaths, with positive scaling of rabies incidence with population size (i.e. more rabies in more populated places) dampening and negative scaling exacerbating the relationship between access and deaths (Fig S6.4A). However, the impact of adding clinics remains broadly the same (Fig S6.4B).

2.6 Discussion

2.6.1 Main findings

We find that the burden of rabies in Madagascar is likely concentrated in areas with poor PEP access. We estimate that current PEP provisioning (at 31 clinics) averts 45% of deaths that would otherwise occur, and that expanding PEP access should reduce mortality, with provisioning in one clinic per district ($N = 83$), or per commune ($N = 1733$), expected to reduce mortality by 16% and 33%, respectively. However, improved PEP provisioning is unlikely to eliminate rabies deaths; with over 600 deaths expected even with PEP at all primary clinics ($N = 1733$). This is partly because travel times remain high (> 2 hrs as estimated by the friction surface for over 10% of the population, Fig S5.4) even after expanding PEP to all primary clinics. With reduced travel times, over 20% of exposures will still not seek PEP (Fig S5.5), resulting in ~ 1.65 rabies deaths per 100,000 people. PEP is expected to remain cost-effective as provisioning expands, to a maximum of 450 USD per death averted (assuming 5 USD per vial), similar to other estimates [4]. While our quantitative predictions depend on assumptions of underlying rabies exposure incidence, the qualitative patterns regarding travel time impacts remain robust and are useful in identifying strategies for provisioning PEP.

2.6.2 Limitations

Data limitations introduced bias and uncertainty to our estimates. For example, travel times from the Malaria Atlas Project friction surface underestimated patient-reported travel times, with discrepancies between assigned transport speeds (from the Open Street Map user community, or country cluster data [18]) and realities of local travel. In Madagascar, the presence of paved roads does not necessarily reflect their quality or the modes of transport used. Patients seeking PEP at the Moramanga clinic reported various transport methods and highly variable travel times even within a single commune. While patient-reported travel times may lack precision from recall and estimation error, they likely better reflect lived experience; validated travel times [30] could improve estimates of spatial health inequities. Similarly, modeled estimates of population distribution [19] also introduce uncertainty. Our analysis of data from the Moramanga District indicates that variation at the sub-district level is high and impacts health seeking behavior. However, we lacked fine-scale data from other catchments for comparison. Additionally, we had to correct for underreporting and incomplete data; strengthening surveillance and routine data collection should improve understanding of health seeking behavior and access, and support monitoring and evaluation of PEP provisioning.

While we rely on a number of assumptions, they are based on data specific to Madagascar or from other similar settings and consistent with estimates from the literature more broadly (see Table 1 and section S4). Our burden estimates were most sensitive to assumptions about rabies exposure incidence, drawn from studies in the Moramanga District [15] and elsewhere [4]. As incidence of rabies exposures varies over time and space [31,32], we incorporated uncertainty into our estimates, but we did not find qualitative differences in the effects of travel times on rabies deaths. Our simplifying assumptions regarding patient compliance, which is generally high in Madagascar [15], and on complete efficacy of PEP are unlikely to greatly influence our burden estimates [22]. Likewise, we do not account for differential risk for severely exposed patients not receiving Immunoglobulins (RIG), which is only available at IPM in the capital of Antananarivo, but recent studies show that even in the absence of RIG, PEP is extremely effective [4]. We also assume that clinics reliably provision PEP, but a 2019 KAP survey reported clinics experiencing stock-outs [25].

We assumed geographic access to PEP was the primary driver of health-seeking behavior, but socioeconomic status, education and awareness about rabies [[33]; [27]; [34]; [35]; castillo2020behavioral] all play a role. For example, most PEP clinics also charge fees (from 0.50 - 3.00 USD for consultations, wound treatment, etc. [25]) which may also act as barriers to PEP access. In Madagascar, where PEP is free-of-charge, the main cost to patients is transport and time lost. More remote communities tend to be of lower socioeconomic and educational status [2], so travel time may be a proxy for these correlated variables. Significant overdispersion in the data that cannot be explained by

travel times suggests that clinic-level variation (e.g. vaccine availability and charges) and regional differences (e.g. dog populations, outbreaks, awareness) further influence health-seeking behavior and vaccine demand. Although our estimates could be improved with better data on rabies incidence, health-seeking behavior, and PEP provisioning, predicting PEP impacts will remain challenging given the complex interactions between socioeconomic factors, access to and quality of care, and human behavior, as illustrated by the case studies in Box 1. However, it is very likely that the impacts of improving access to PEP could be further increased with outreach and awareness raising efforts that we were unable to parameterize.

2.6.2.1 Box 2: case studies of of health seeking behavior for PEP in Madagascar

1. Anosibe An'ala District (population ~ 100,265), south of Moramanga, has moderate incidence of bite patients (~ 54/100,000 persons) even though travel times often exceed 24 hours. While a road connects the main Anosibe An'ala commune to the Moramanga PEP clinic, it is only passable by large trucks during much of the rainy season, with speeds usually < 10km per hour. Over 9% of patients from Anosibe An'ala had been in close proximity or touched a person that died from rabies (four suspect human rabies deaths of patients who did not receive any PEP), whilst of patients with Category II and III exposures that were interviewed, 11/19 (58%) were bitten by probable rabid dogs. Given the high travel times (although underestimated by the friction surface) and incidence of reported rabies exposures and deaths, we predict a large but unobserved rabies burden in this remote community (~6.02 deaths per year) and we ranked a clinic provisioning PEP in Anosibe An'ala 28th for travel time reductions. Other remote communities likely experience similar high and unrecognized burden, but improved surveillance is necessary to identify such areas. Notably, bite patients in this district demonstrate willingness to travel for free PEP (in some cases walking 3 days to a clinic) with awareness of rabies risk. Community outreach and active surveillance in other remote areas could also greatly improve people's awareness of risk and health seeking behavior.
2. Recently, a middle-aged taxi driver died of rabies in suburban Antananarivo. The day after being bitten by an unknown dog, he reported to a clinic that referred him to the closest clinic provisioning PEP, approximately one hour's drive from his home. His family urged him to go, but he did not believe his risk was high and decided not to seek further care. He developed symptoms two weeks later and was confirmed as a rabies death by the National Rabies Reference Laboratory. Despite prompt reporting, appropriate referral, and socioeconomic indicators suggesting a high care-seeking probability, this person did not receive PEP. His story highlights the need for sensitization about rabies, how PEP provisioning at peripheral clinics (even in

areas with reasonable access) could prevent additional deaths, and ultimately that PEP alone is unlikely to prevent all rabies deaths.

2.6.3 Broader context

Recent studies have estimated access to health-seeking behavior and PEP completion and adherence, but not directly linked these estimates to burden [7,36,37]. Our approach for incorporating access to vaccines (echoing [38–42]) into burden estimation methods could guide provisioning of PEP to maximize impacts. This approach will have most value in settings with limited PEP access and poor health seeking, but will be less valuable where rabies exposures make up a small fraction of patients reporting for PEP e.g. [43,44]. In other settings, similar statistical approaches could be used to identify and quantify key barriers to PEP seeking behavior. For example, reducing the direct cost of PEP is likely to be of more importance than increasing geographic access where PEP costs are high.

Our revised estimate of rabies deaths in Madagascar using this approach was higher than previously estimated (between 280 - 750 deaths/year) [15], which assumed uniform reporting of 85%, but remained within the range of other empirical and modeling studies from low-income countries [26,27,45–47]. Our estimates of vial demand depend on use of the new abridged intradermal regimen [28], which has been adopted by the Ministry of Health in Madagascar. However, most clinic staff were not aware of WHO classifications of exposure categories, and vaccination of Category I exposures (those not requiring PEP) remains common practice, comprising 20% of vial demand in Moramanga [15].

We predict that as clinics are expanded, throughput (daily patients reporting to a clinic) will decrease. This may complicate the supply chain and make provisioning PEP more challenging as vial demand becomes less predictable, leading to stock outs or wastage. Decentralized provisioning mechanisms, for example adopting routine childhood vaccine supply chains, or novel vaccine delivery methods such as drones [48], may mitigate these challenges. When nerve tissue vaccines were used in Madagascar, clinics requested vaccines upon demand and PEP access was more widespread, but provisioning the more expensive cell culture vaccines to all clinics became too costly [16]. Widespread vaccine provisioning is therefore feasible given Madagascar's health infrastructure, if cost barriers are removed.

Gavi investment could greatly reduce the access and cost barriers to PEP [6,7,22,49]. Currently, each clinic in Madagascar serves an average catchment of 780,000 persons. Latin American countries, where significant progress has been made towards elimination, aim for one PEP clinic per 100,000 persons. In Madagascar this would require around 212 additional clinics provisioning PEP. We predict that Gavi investment would be highly cost-effective, greatly reducing deaths by expanding PEP supply to underserved areas.

However, our results suggest that PEP expansion alone cannot prevent the majority of rabies deaths, and even given maximal access, achieving ‘the last mile,’ preventing deaths in the most remote populations, will require disproportionate resources [50]. To achieve ‘Zero by 30,’ mass dog vaccination will be key to interrupting transmission and eliminating deaths. Integrated Bite Case Management (IBCM) uses bite patient risk assessments to determine rabies exposure status, guide PEP administration, and trigger investigations of rabid animals, potentially identifying other exposed persons [15,51,52]. IBCM is one way to manage PEP effectively [43] and as it relies on exposed persons reporting to clinics, expanding PEP access could strengthen this surveillance framework. These same issues of access, however, apply to both dog vaccination and surveillance, and understanding spatial heterogeneities will be critical to determining how control and prevention interventions can be best implemented [53,54].

2.7 Conclusion

Our study suggests that rabies deaths in Madagascar disproportionately occur in communities with the poorest access to PEP and that expanding PEP access should reduce deaths. Without data on rabies incidence and exposure risk, targeting PEP expansion to underserved areas is a strategic way to reduce rabies burden and provide equitable access, for example, by expanding provisioning to clinics serving populations that target an evidence-based travel time threshold or catchment size. Implementing outreach programs to raise awareness should further increase the efficacy of PEP expansion by improving care seeking. Better surveillance is also needed to understand the geographical distribution of rabies exposures and identify populations most at risk, and to evaluate the effectiveness of PEP expansion at preventing human rabies deaths. Gavi investment could support countries to more equitably provision PEP and overcome barriers to access ([9], see Box 1 for case studies), but as PEP alone cannot prevent all rabies deaths, investment should be used to catalyze mass dog vaccination to interrupt transmission, and eventually eliminate rabies deaths.

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2.9 Supplementary Appendices

All supplementary figures and tables can be viewed with the full manuscript at this link: <https://mrajeev08.github.io/MadaAccess/>. A link to the supplementary materials will be included in this dissertation once published.

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Chapter 3

Modeling canine rabies virus transmission dynamics

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3.1 Abstract

Mathematical models of infectious disease are used to develop an understanding of disease dynamics and aid in designing control strategies. Modeling can also shed light on how dynamics, and therefore intervention strategies, may change as control is implemented. In light of the mounting evidence that elimination of canine rabies is a realistic objective, the WHO has set a global target of zero human deaths due to dog-mediated rabies by 2030. In this chapter, we focus on how dynamic epidemiological modeling can guide efforts to achieve this goal. We review existing modeling work and identify insights generated, outstanding questions, and gaps in our knowledge. We further discuss the role that modeling can play in the future to inform elimination.

Key Words: Canine rabies, Zero by 30, disease modeling, mass dog vaccination, transmission dynamics

3.2 Introduction

Models of disease dynamics are a powerful tool in the arsenal of disease prevention and control efforts, and can be used to estimate key epidemiological parameters, establish targets for control, and guide policy [1]. Modeling can also identify counter-intuitive outcomes that emerge as interventions are implemented, and challenges in the endgame when disproportionate resources are necessary to reach the last mile of elimination [2]. In light of the global goal to eliminate human deaths due to dog-mediated rabies by 2030, models of rabies virus transmission have potential to inform control efforts as countries progress towards elimination.

3.2.1 History of modeling rabies virus transmission dynamics

Modeling rabies in domestic dog populations is a relatively nascent effort. In contrast, models of wildlife rabies guided early control efforts [3]. Elimination of fox rabies in Europe was kick-started by modeling studies that demonstrated the feasibility of control [4]. Surveillance of rabies in wildlife systems in Europe and North America provided rich data sets to characterize dynamics, identifying the wave front of outbreaks to target control geographically [5], establishing that landscape features such as rivers act as barriers to disease dispersal [6], and delineating how birth pulses shape seasonality in transmission [7]. This work provides a foundation for modeling canine rabies, but there are fundamental differences between wildlife and domestic dog systems. Human populations, behavior, and culture structure dog populations [8]. In addition, canine rabies persists in low- and middle-income countries where surveillance capacity is limited and representative disease data are lacking [9]. Beyond capturing core infection biology, models of canine rabies must also encompass human influences and be tractable to interpretation in data-sparse settings.

3.2.2 The modeling backbone for canine rabies

Rabies can be modeled in an **SEIV** framework, with **Susceptible**, **Exposed**, **Infectious**, and **Vaccinated** classes (Figure 20.1). Dog demography governs the dynamics of the susceptible and vaccinated classes. The **Susceptible** population is replenished by births and depleted by mortality (both natural and disease-induced) and vaccination. The **Vaccinated** population is governed by the rate of vaccination, but depleted by natural mortality and waning of immunity generated by vaccines (most high quality vaccines are protective for at least 3 years, [10]. For canine rabies, evidence suggests that domestic dogs are the reservoir host even in areas with complex wild carnivore communities [11], [12]. While other wildlife hosts may contribute to transmission, single-host models of rabies in the

dog population are likely sufficient to understanding and predicting dynamics in most endemic areas [13].

Rabies virus is directly transmitted, typically via bites, in the saliva of infectious animals. Transmission is on average low: most dogs do not transmit or only infect one or two other dogs. However, there is also substantial heterogeneity in transmission, and some dogs are capable of biting upwards of 20 other dogs during their short infectious period [14]. The incubation period is about 21 days but is highly variable. Most exposed dogs become infectious within one month, but some infections manifest months after initial exposure [14]-[16]. The infectious period, on the other hand, is predictably short, and infection results in death generally within 10 days of showing neurological signs of infection [14], [17]. There is little evidence that individuals can be infectious but subclinical (i.e. no carrier class), and there is no recovered class, as exposure does not confer immunity [18], and following onset of clinical signs, rabies is invariably fatal.

Although transmission is mostly local (< 1 km), rabies can cause erratic and unpredictable behavior, with infected dogs able to run more than 15 km, beyond the typical home range of most healthy dogs [14]. As a result, secondary cases often occur from disease-mediated incursions spread from neighboring populations (e.g., nearby populated settlements within the range of rabid dog movement). In addition, long-distance human-mediated incursions of incubating dogs can result in outbreaks being seeded from otherwise unconnected populations [19].

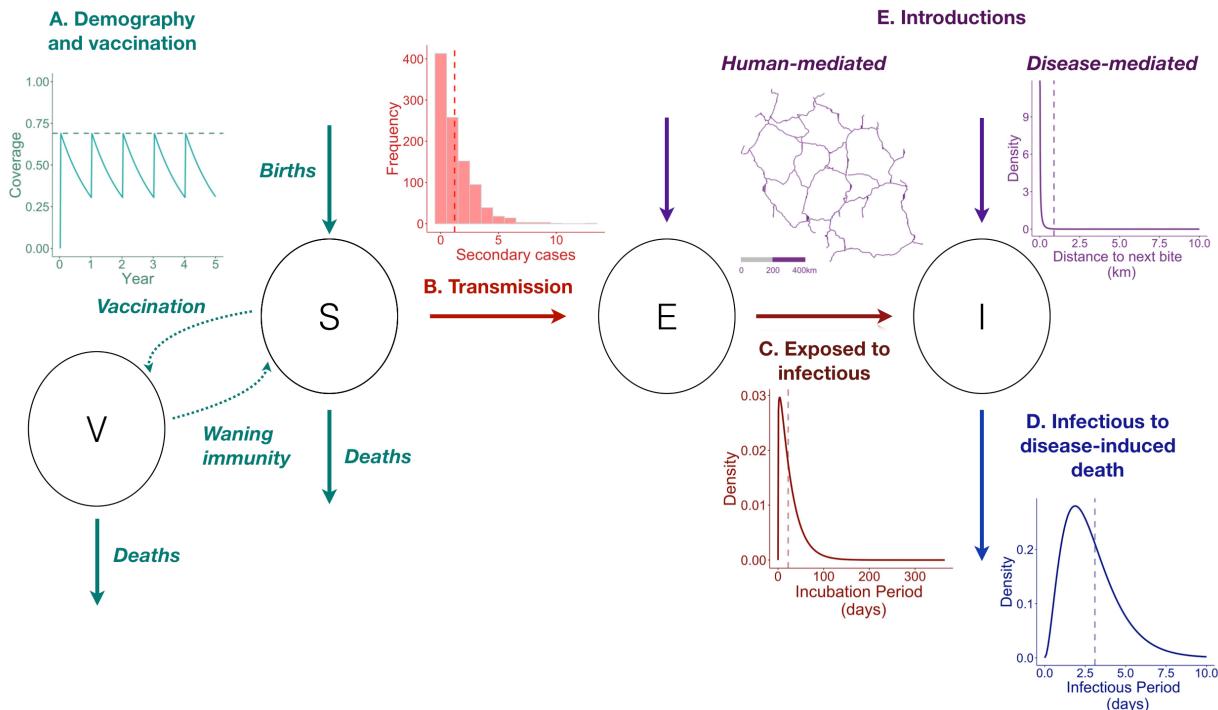


Figure 20.1. The Susceptible-Exposed-Infectious-Vaccinated (SEIV) modeling framework for canine rabies: circles indicate epidemiological classes, arrows linking circles indicate how individuals can move between classes, insets describe underlying processes and influences. **A)** **Host demography (i.e., the balance between births and deaths) and vaccination** govern the susceptible and vaccinated population dynamics. Following vaccination campaigns, vaccination coverage (y axis, inset) first increases (vertical jumps) then wanes over time (x axis) as vaccinated individuals die, susceptible individuals are born, or as immunity conferred by vaccination wanes (in this example, campaigns reach 70% of the population annually, but coverage wanes to approximately 35% before the next annual campaign). **B)** **Transmission** is on average low, but highly heterogeneous. Inset shows number of secondary cases generated from a negative binomial distribution ($n = 1000$ draws, mean number of secondary cases = 1.2, red dashed line). **C)** Individuals move from **exposed to infectious** on average after 22.3 days (inset, dashed line) but this is also highly variable with some infections occurring months to years after exposure. **D)** **Disease-induced mortality** is complete, and the infectious period is short, on average 3.1 days (dashed line), with deaths due to infection occurring within 10 days. **E)** **Introductions** from outside the population modeled may seed cases within. Introductions may result from **disease-mediated** movement of infectious dogs (sometimes upwards of 10 km; inset shows dispersal kernel, gamma distribution) and **human-mediated** movements of incubating dogs (potentially on the scale of 100s of km through movement along roads; the

inset shows an example of a major road network in Tanzania). All parameters used and associated references are listed in Table 20.1*

Table 20.1 Key parameter values associated with underlying processes illustrated in Figure 20.1

Process	Distribution	Parameters	Value	Source	Inset
Birth rate	–	Mean annual rate (dogs/yr)	0.5	[20]	A
Death rate	–	Mean annual rate (dogs/yr)	0.42	[20]	A
Vaccine waning	–	Mean annual rate (dogs/yr)	0.33	[10]	A
Secondary cases (R_0)	Negative binomial, mean 1.2 secondary cases	Mean Dispersion parameter (k)	1.2 1.3	Townsend et al., 2013	B
Incubation period	Gamma, mean 22.3 days	Shape Rate	1.15 0.04	Hampson et al., 2009	C
Infectious period	Gamma, mean 3.1 days	Shape Rate	2.9 1.01	Hampson et al., 2009	D
Dispersal kernel	Gamma, mean 0.88 km	Shape Rate	0.215 0.245	Townsend et al., 2013	E

3.3 How to model rabies virus transmission?

There has been considerable debate about how to model rabies virus transmission, which echoes a larger debate within the disease ecology community [21]. Theory indicates that for diseases with density-dependent transmission, i.e. when transmission scales with host density, there exists a thresh-

old density below which the disease cannot persist [22]. However, there is no such threshold when transmission is frequency-dependent, i.e. transmission rates are independent of host density [21].

For canine rabies, the basic reproductive number (R_o) or the average number of secondary cases resulting from a single infection in a completely susceptible population, is generally estimated as between 1-2 [14], [23]-[25]. Such consistently low estimates of R_0 across a range of dog densities suggest that rabies virus transmission is largely frequency-dependent [14], [24], [26]-[28]. That is, rabid dogs have on average the same number of infectious contacts regardless of the density of dogs around them. As a result, reductions in population densities are not likely to be effective in eliminating rabies. In practice, although a common practice and one predicated on assumptions of density-dependent transmission, indeterminate culling of dogs does not curtail rabies transmission [29].

Despite evidence for frequency-dependent transmission, many modeling studies formulate rabies transmission as density-dependent (Figure 20.2D). For a given R_0 , this assumption of density-dependent transmission does not impact herd immunity thresholds; the critical proportion that needs to be vaccinated, p_c , is equal to $1 - 1/R_0$ regardless of the form of transmission [22]. However density-dependent models predict reductions in transmission due to declining dog density (e.g., via culling or disease-induced mortality) that are unlikely to translate to the real world.

Models with frequency-dependent transmission are also not entirely consistent with empirical observations. Frequency-dependent models that assume homogeneous mixing (i.e. equal contact probabilities between all individuals in a population, also referred to as ‘mass action’) result in eventual population extinction for fatal pathogens like rabies [30]. Only under very low transmission (1.01-1.02) and high population growth can rabies persist in models with frequency-dependent transmission. For models with density-dependent transmission, even with R_0 between 1.01 and 1.1, models of rabies show high annual incidence (Supplemental Figure 1), which is at odds with empirical evidence. Where measured, rabies incidence is low (< 1-2% annually) and consequently has little demographic impact on dog populations [31]. Additional model structure is therefore necessary to explain how rabies can persist at such low incidence.

Transmission heterogeneity may be a potential mechanism to explain the relatively low incidence of rabies. A high proportion of dead-end or singleton transmissions result in negligible depletion of susceptibles, while occasional superspreaders may seed and maintain transmission. In addition to unrealistic estimates of rabies incidence, if heterogeneity in transmission is not captured, there is a risk that models may generate biased estimates of control indicators, such as the time to elimination and the threshold level of vaccination that this requires.

Accounting for the spatial scale of transmission could also explain how rabies persists at low incidence. As most transmission occurs within a 1 km radius of infected animals, susceptible depletion

at such fine scales may limit transmission in a way that is not captured in mass action models [32]. Phenomenological approximations may offer a solution to this challenge [33], [34], but have yet to be thoroughly explored for rabies. Spatially-explicit individual-based models implemented at the scale at which most mixing occurs generate more realistic dynamics [24], [35], but are computationally intensive and not analytically tractable. Nonetheless, such models provide insights into underlying mechanisms that could be simplified for more expedient models. Finally, human behavior has also been implicated in curtailing epidemics, with responses such as tying and killing infectious dogs and reactive vaccination thought to scale with incidence [36].

There is limited data to disentangle these potential mechanisms, which could reconcile empirical observations with modeling results. Further work is necessary to ensure sufficient model realism to inform policy, but balancing realism and complexity is a key challenge for any modeling study [37]. Building in realism requires additional parameterization and, often, additional assumptions. Robust epidemiological and biological data are therefore key to improving our understanding of how to model rabies transmission.

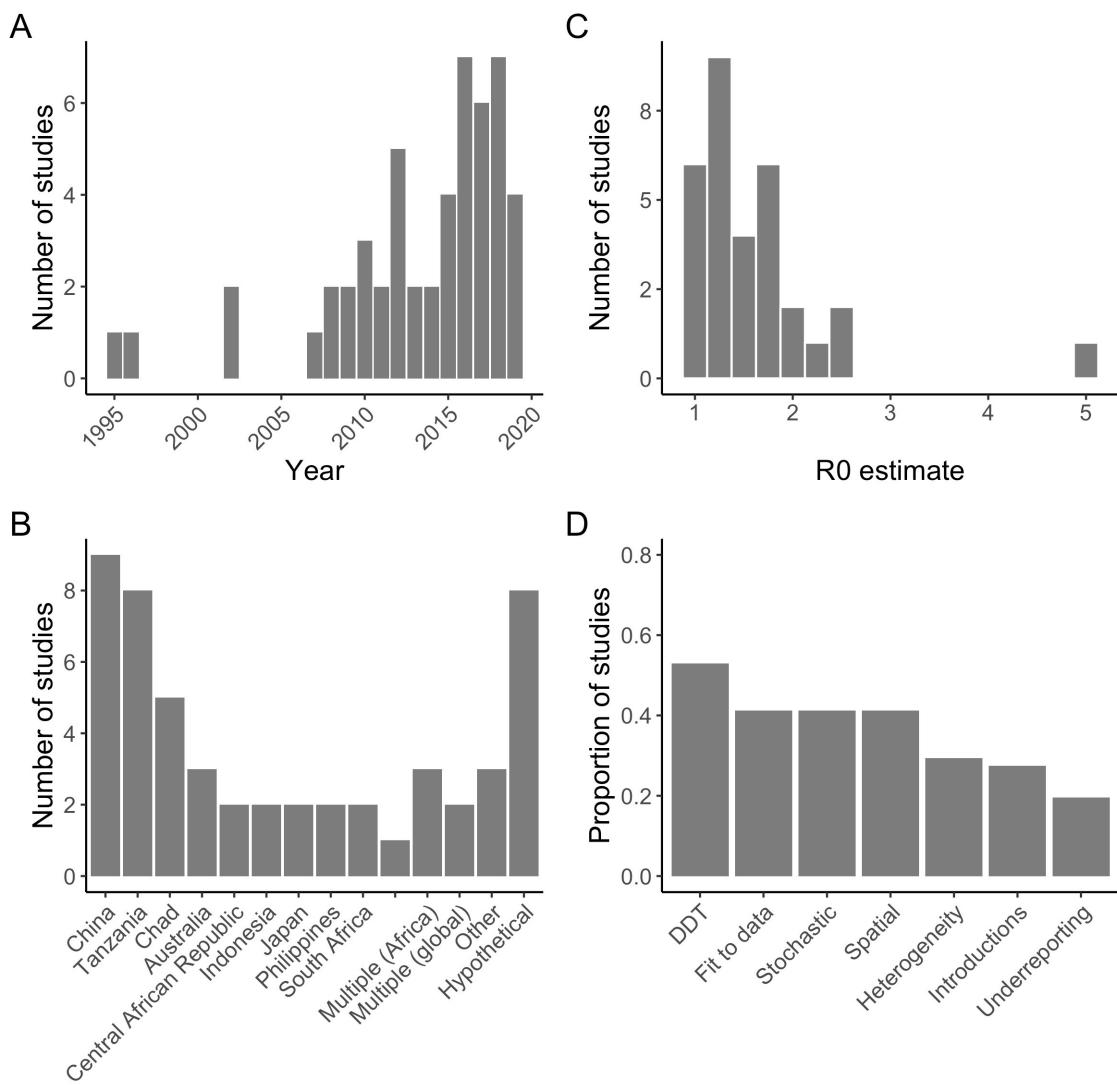


Figure 20.2. Summary of studies with a dynamic model of canine rabies. A total of 51 studies were included. A) Year of publication, with most studies published after 2006; B) Countries where rabies dynamics were modeled: studies were concentrated in China, Tanzania, and Chad, but many also examined dynamics in hypothetical contexts, not specific to any geographic situation. C) Estimates of R_0 : most studies estimated R_0 below 2 (10 studies, with 31 estimates); estimates of R_e (the effective reproduction number which accounts for ongoing vaccination) and R_t (time-varying reproductive number) were excluded ($N = 3$). D) Key features of models ($N = 51$): most assumed density-dependent transmission ($N = 27$). Less than half were fit to data ($N = 20$), stochastic ($N = 20$), or spatially-explicit ($N = 19$). 15/51 studies incorporated individual heterogeneity in transmission and 14/51 introductions from outside the population modeled. Only 10 included an observation model in their analysis or accounted for underreporting in their inference. Full bibliography and metadata included in Supplementary Table 1.*

3.4 Existing Modeling Studies

Two systematic reviews of rabies models recently examined the effectiveness and cost-effectiveness of control and prevention strategies. They concluded that estimates of R_0 are consistently below 2 and dog vaccination is an effective strategy, but vaccination coverage is critically influenced by dog demography [38]. Both mass dog vaccination and provisioning of PEP to bite patients are cost-effective, in contrast to dog culling which has rarely been identified as either economically feasible or effective [39]. Building off these reviews, we examined studies with a dynamic modeling component and synthesized insights generated and data used to inform them. We searched for papers that had the terms “rabies” AND (“domestic dog*” OR “canine”) AND “model*” on PubMed and Scopus, including all English language papers published between January 1995 and July 2019 that incorporated a transmission model of rabies virus in domestic dogs. Of the 547 unique records retrieved, 51 papers fitted these inclusion criteria (Figure 20.3, Supplementary Table S1).

3.4.1 Insights and limitations

Of studies that compared intervention strategies (generally: mass dog vaccination, human PEP provisioning, and dog population control including culling), the majority show that dog vaccination is most effective, and essential to achieve elimination. Despite the potential to maximize population-level immunity, synchronizing vaccination campaigns geographically had little impact on probability of elimination, at least for annual vaccination campaigns. In contrast, spatial heterogeneity in vaccination coverage had a greater impact, with even small contiguous coverage gaps reducing the probability of rabies being eliminated [24], [35].

While the critical vaccination threshold (p_c or $1 - 1/R_o$) should theoretically be much lower than 70% for a disease with the low range of R_0 estimated for rabies (Figure 20.2C), the coverage level recommended by WHO reflects an empirical consensus [23], [40]. Models show that due to high turnover in domestic dog populations, annual campaigns that reach at least 70% of the population are necessary to maintain coverage > 20% throughout the year. Furthermore, heterogeneity in transmission and frequent introductions of rabies cases increase both the vaccination threshold necessary to interrupt transmission, and the probability of observing small outbreaks even when vaccination coverage is high [14], [41].

Most published models were deterministic (33/51) and did not incorporate heterogeneities in transmission (36/51, Figure 20.2D). However, as R_0 for rabies appears to be low, the interaction between stochasticity and heterogeneity in transmission may be influential. In general, for diseases with high transmissibility (i.e. measles), heterogeneities in transmission can often be ignored as these complex-

ties have little impact on the emergent dynamics of infection [30]. However, for a disease with lower transmission, heterogeneities may result in unpredictable outbreaks [37]. Stochasticity is especially crucial in the endgame, when elimination probabilities and incursion dynamics depend on rare events.

Most studies model rabies virus transmission in a closed population, that is without introductions from neighboring areas (Figure 20.2D). While this is a reasonable approach in island settings such as in Bali, Indonesia [24], recent modeling and phylogenetic work shows the importance of incursions in less isolated populations in sustaining rabies virus transmission (Bourhy et al., 2016; Zinsstag et al., 2017) and that multiple strains co-circulate within a population [42], [43]. Human behavior is also a key driver of transmission patterns, facilitating as well as dampening transmission [44]. Multiple studies have found signals of long distance transmission beyond the range of disease-mediated dispersal, showing the role of human-mediated movement of incubating dogs [44]-[46]. Road networks have been identified as correlates of phylogenetic distance, indicating that human movement could shape the spatial structure of canine rabies virus [44]-[46]. There is also strong phylogenetic evidence that historical human-mediated long-distance movements underlie much of the contemporary global distribution of canine rabies [47]. This work emphasizes the need to understand how the size and connectivity of populations affects the persistence of disease. Models have productively explored this historically important question for childhood infections such as measles [48], but for canine rabies, this remains an important challenge, which may well define progress towards elimination.

A few studies look at how contact networks and movement behaviors could drive transmission [49]-[51]. These studies simulated outbreaks on contacts networks constructed using data from healthy domestic dogs. They found that in general, targeting highly connected dogs or dogs with larger home ranges for vaccination results in a higher probability of disease elimination, but few predictors of connectivity of individuals emerged. Broadly, these results are consistent with previous work on transmission heterogeneity and could bring valuable benefits if it were possible to *a priori* identify and target high-risk animals. However, these traits are difficult to estimate in most endemic settings, where there is limited data on dog populations, let alone individual dog traits. Moreover, as rabies causes severe neurological symptoms, the validity of these findings depends on how representative data from healthy dogs are of movement and contact patterns of rabid dogs.

Dynamic models have been integrated with economic models to estimate cost-effectiveness of interventions, demand for rabies PEP, and disease burden. Early cost-effectiveness models critically lacked data on the costs of PEP for those seeking care for non-rabid dog bites [27], [52], [53]. Decision tree models have addressed these issues and provide a framework to integrate field data on rabies exposures, health-seeking, and access and adherence to PEP into estimates of burden [54]-[56]. These more recent studies demonstrate that PEP is still a very cost-effective intervention even when ac-

counting for management of patients bitten by non-rabid animals and emphasize the potential value of administering rabies vaccine intradermally using the latest WHO recommended abridged regimens [57]. However, they also highlight two other critical points for policy. First, without strategies for more judicious use, costs of PEP will remain high and continue to rise even when dog rabies is controlled. Moreover, human rabies deaths will continue to occur and the target of zero deaths by 2030 cannot be achieved through PEP alone. A massive scaling up of dog vaccination is required in most endemic countries. Support for human rabies vaccines through Gavi, the Vaccine Alliance, is therefore a promising step towards the 2030 goal [56], but more investment and commitment is still needed.

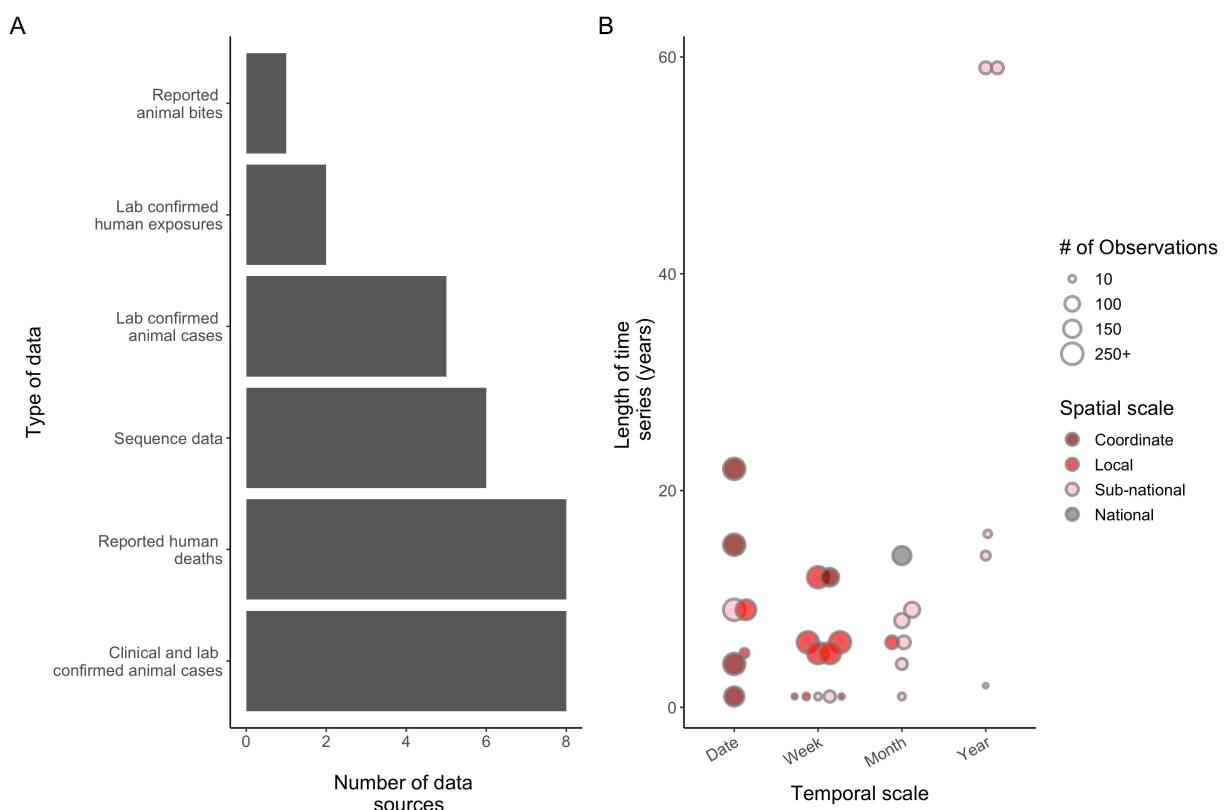


Figure 20.3. Rabies data reported in modeling studies ($N = 25$ studies reporting 30 unique data sources). A) Type of data used. B) The scales of temporal (x-axis) and spatial (colors) information available and the duration (y axis). The size of the points is proportional to the number of observations in each data set. Any rabies data that was reported in studies were included (even if not used for fitting purposes, only for qualitative comparison). If multiple data sets were used, they were included as separate data sources, and if the same data set was used in multiple studies it was only included once.*

3.5 The gap between models and data

Despite limited surveillance, few studies incorporated observation models into their analyses or conducted sensitivity analyses on how underreporting might bias their inferences (Figure 20.2D). Developing models of the observation process and integrating them into dynamic models (often termed state-space modeling, [58]-[60] is essential when fitting to incomplete data. But, these modeling frameworks can also guide surveillance strategies across the elimination timeline by estimating the minimum detection levels and time necessary to verify elimination [61].

A major limitation of many existing modeling studies is a lack of data to inform conclusions, with less than 40% of models fit to data (Figure 20.2D). For studies which did report incidence data, the scale and quality of the data also varied greatly. Human deaths reported at the national or regional level and numbers of clinical and laboratory confirmed animal cases were the most commonly used data (Figure 20.3A). The number of observations and length of the time series varied greatly, from over 1000+ observations at a fine spatiotemporal scale over a 15-year period to annual cases reported for only 2 years (Figure 20.3B). Ultimately, integrating data on rabies incidence and dog populations into models of transmission is a critical step to moving modeling efforts forward. Below we describe the various data sources that can be used to fit and inform models and associated challenges and solutions to collecting this data.

3.5.1 Bite data

Bite data, (i.e. data on patients seeking care for animal bites) are often used as a proxy for rabies exposure incidence. However, these data often lack details on the status of the biting animal and are heavily skewed by who has access to care, both geographically and socioeconomically. Paradoxically, in settings where the direct cost of PEP is charged to patients, bite records may be more reflective of rabies exposures: people may be less likely to seek care when the perceived risk is low (i.e. fewer people seek care for provoked bites by known healthy and/or vaccinated animals) due to the associated costs [62], [63]. In settings where PEP is provided for free and indiscriminately, a higher proportion of reported bites may be due to non-rabid animals [64]-[66], and many Category 1 exposures, i.e. those for which PEP is not indicated [67], receive unnecessary PEP [66], [68], [69].

For data on bite patients to be more useful for modeling and surveillance purposes, supplementary information for each bite beyond the date reported and number of doses received is needed. Categorizing the type of exposure per the WHO categories can help to exclude Category 1 exposures. Reporting clinical signs and the outcome of the biting animal at each patient visit can identify probable rabies exposures and trigger field investigations and sample collection to improve surveillance.

Finally, information on the geographical location where the patient was bitten, for example to the finest scale administrative unit identifiable, could be used to understand spatial patterns of transmission, estimate demand for PEP, and identify determinants of health seeking behavior.

3.5.2 Laboratory confirmed case data

Laboratory confirmed case data are considered a gold standard due to the high sensitivity and specificity of diagnostic tests for rabies, but represent the tip of the iceberg in terms of true incidence [9], [61]. Diagnostic confirmation of rabies cases is often lacking in many endemic settings due to limited laboratory and field capacity. Even with strong laboratory resources in country, collecting a brain sample from a suspected rabid animal or human case can be challenging. Lack of cold chain and accessibility to communities, limited veterinary capacity and training in euthanasia and sampling methods, and low reporting of suspected cases are all significant barriers to case confirmation. For humans, nuchal samples can be collected non-invasively (from nape of the neck) to confirm a rabies case ante-mortem [70]. However, confirmation of a human case first requires a person to seek care, and rabies deaths are most common in populations with the least access to health care [71]. For animal cases, field sample collection methods, like the straw method of sampling brain tissue that does not require the submission of the whole head, and alternative forms of sample storage and testing, such as rapid diagnostic tests and filter papers, have potential to address some of these challenges [72]. While these alternative tests may not be appropriate for guiding patient treatment, they could greatly improve surveillance and understanding of rabies virus transmission if implemented more routinely.

Even with the gold-standard diagnostic test, using laboratory confirmation to guide administration of PEP in endemic settings may be impractical, due to delays in sampling and testing. Integrated bite case management (IBCM, see Chapter 18) programs, which combine risk assessments, field investigations, animal observation/quarantine, and sampling of suspected cases, are a promising method of improving rabies surveillance and PEP provisioning. IBCM can increase both detection of and confirmation of clinically suspect animal cases and guide referrals for PEP , as well as limit further exposures by euthanizing rabid animals once detected [73]. However, IBCM relies on coordination between human and animal health practitioners and resources to support clinical rabies diagnosis and field sample collection, which is still lacking in most low-income countries.

3.5.3 Sequence data

Sequence data can be used to make inferences about transmission processes, particularly when linked with epidemiological data [43]-[45], [60], [74], [75]. Recent studies have demonstrated the added value

of whole-genome sequencing (WGS) for understanding finer scale transmission dynamics of canine rabies [44], [74], but WGS has yet to be routinely generated for canine rabies. Sequencing capacity is even more limited than general laboratory capacity in rabies-endemic countries and exporting samples for sequencing is costly. Advances in portable, real-time sequencing could help to tackle these limitations in the field (ARTICnetwork, <http://artic.network/index.html>). Portable sequencers such as the MinION could support rapid generation and dissemination of sequence data. Methods to sequence from alternative sample types, such as rapid diagnostic tests and filter papers, could also help to overcome obstacles in field sample collection and transport [72]. Bioinformatic pipelines and open sharing of sequences, such as those developed for other viral pathogens [76], could greatly facilitate our understanding of rabies dynamics at a regional and global scale. In general, low-cost, high-throughput sequencing methods should be developed to increase the timely availability of representative sequence data from endemic settings.

3.5.4 Dog population and vaccination data

Data on the dog population is necessary to further understand how the distribution, density, and connectivity of the host population drives transmission [74]. Estimates of vaccination coverage and other intervention efforts facilitate inference of the mechanisms driving transmission and the impact of interventions, helping to predict future outcomes given different control strategies [75]. In most endemic countries, limited systematic data is collected on dog populations. If integrated into more routine census or demographic surveys (i.e. the Demographic and Health Surveys, <https://dhsprogram.com>), questions on dog ownership and vaccination status at the household level could be a potential way to get this data where the majority of the dog population is owned. However, if conducted as standalone surveys, these can be resource intensive and difficult to implement in a representative way, particularly in more rural/remote areas. Alternatively, integrating post-vaccination coverage surveys into campaigns has been shown to be a cost-effective way to generate coverage and population estimates, and only requires temporary marking of vaccinated dogs [77]-[79]. As spatial heterogeneity in coverage is likely a key factor driving the success of vaccination campaigns, such coverage estimates at the scale at which campaigns are implemented could be critical to understanding rabies persistence and elimination probabilities.

3.6 Conclusions

Modeling studies, in combination with decades of empirical evidence, have demonstrated that dog vaccination is the optimal intervention strategy for controlling canine rabies. As global momentum

for implementing national rabies control programs grows, models should move beyond comparing vaccination and other strategies in idealized populations towards linking models with field data to identify refinements to intervention strategies. To date, most work has focused on studying control efforts and identifying drivers of dynamics (often without using data), and studies of the impact of control have rarely been linked to analyses grounded in empirical data (i.e. studies that explained observed patterns or estimated key parameters, see Supplementary Figure 2 for an overview of existing studies). Models should aim to integrate these questions and test specific vaccination strategies, such as ring vaccination or establishment of control corridors based on geographic barriers as implemented for wildlife rabies in Europe.

Key parameters to estimate from models and data include transmission heterogeneity (captured in the distribution of secondary cases), the dispersal kernel, and introduction rates (including how to differentiate ongoing local transmission from imported cases). Integrating models of surveillance into dynamic models can further establish surveillance requirements necessary to verify freedom from disease and inform policy decisions regarding the cessation and scaling back of control efforts. Importantly, models can predict how these requirements might change over the elimination timeline. Given the challenges in generating high-quality surveillance data for canine rabies, these models can also be used to account for underreporting and determine the minimum level of detection necessary for robust inference. Phylodynamic approaches, which combine both epidemiological and genetic data, are a promising avenue to tackle many of these questions. Critically, progress in this area will require strong surveillance systems and representative data from a range of populations.

Countries have made varying progress towards elimination, ranging from some that lack a realized national control policy and others in the end-game stages of elimination. Now, we are tasked with building flexible models that can capture rabies dynamics and the impacts of control across the elimination timeline. Identifying where and how implementation of control efforts needs improving and delivering such improvements will require a much closer collaboration between scientists, practitioners and policymakers.

3.7 Data and code availability

All data and code used to generate figures and supplemental files, as well as the bibliography for the literature review are available online at <https://github.com/mrajeev08/ModelingChapter>.

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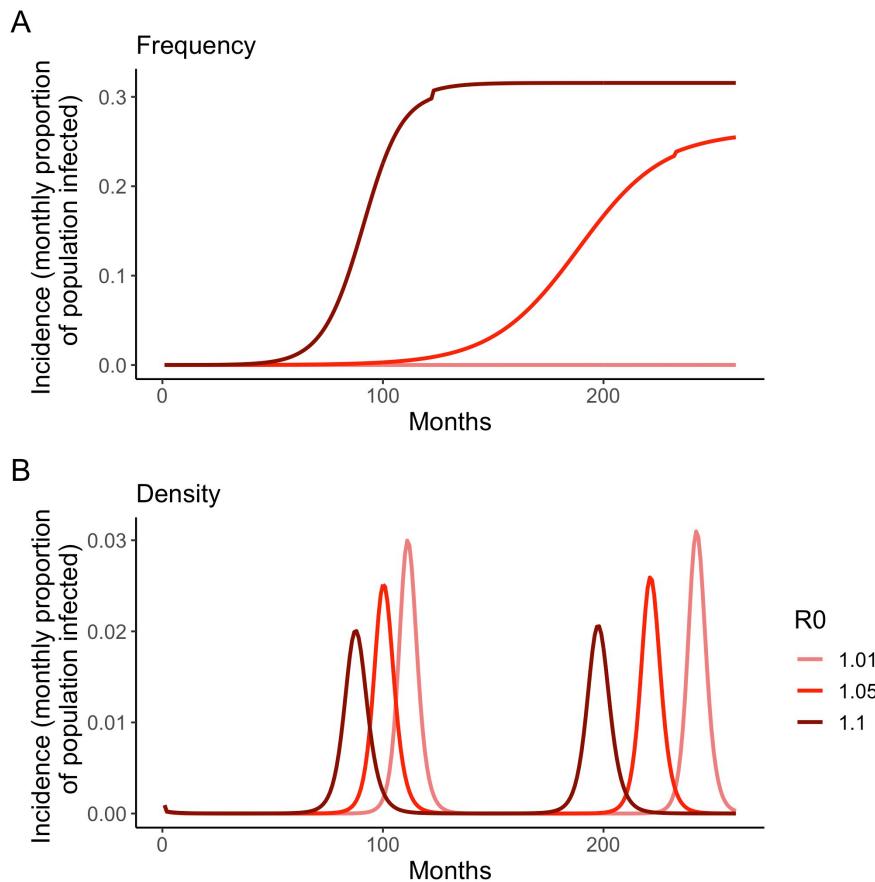
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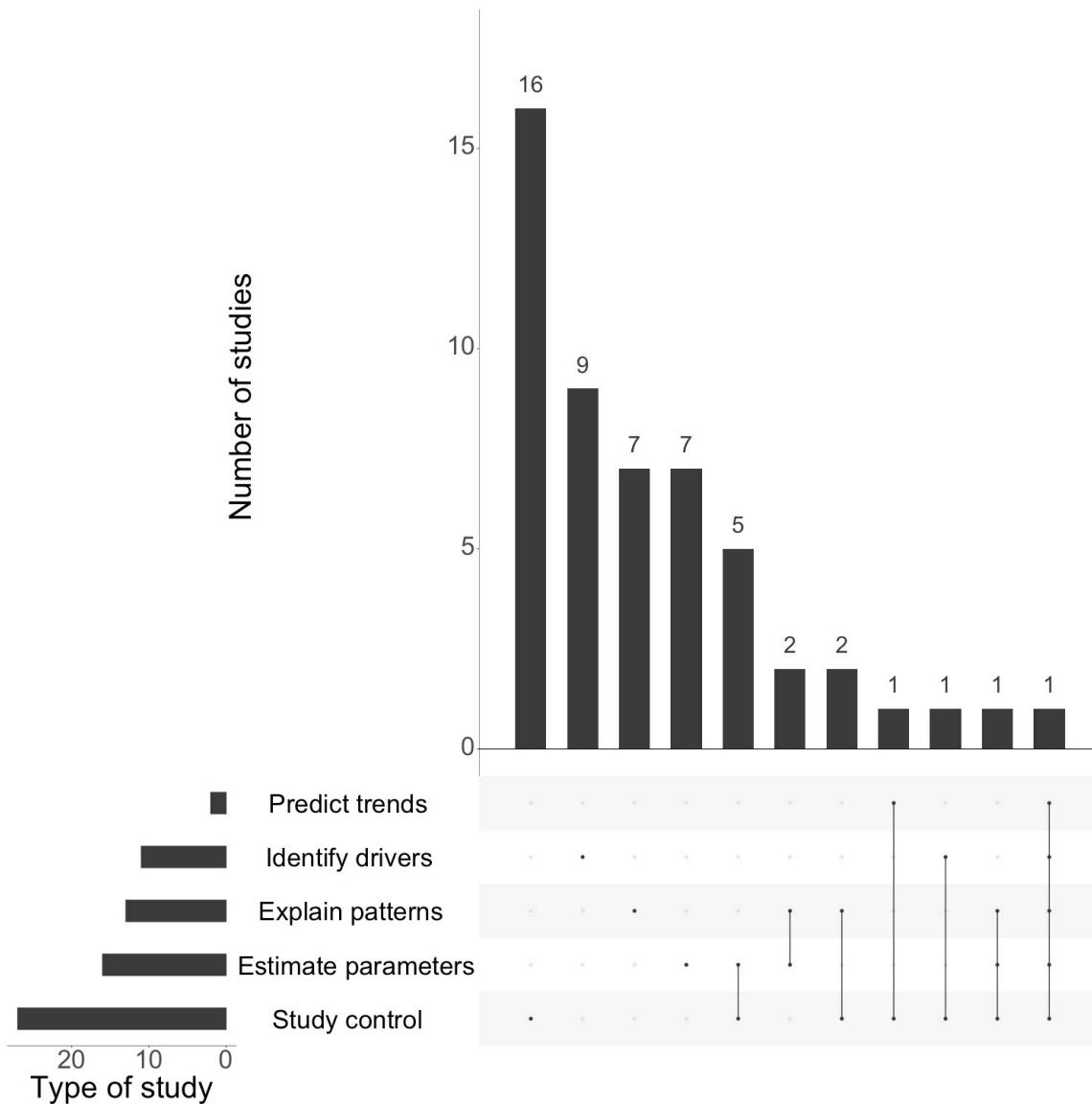
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3.9 Supplementary Figures



Supplemental Figure 1. Density vs. frequency-dependent transmission. Monthly incidence (the proportion of the population infected, and thus removed (as a result of mortality)) from mass-action models of rabies with A) frequency and B) density dependent transmission. Even in low transmission scenarios ($R_0 = 1.01 - 1.1$), incidence peaks at between 1.5 – 2.0% per month for models with density-dependent transmission and between 0.01 - 30% for frequency-dependent transmission, compared with the 1 - 2% max annual incidence observed empirically. Demographic and transmission parameters are listed in Table 20.1 (mean incubation and infectious periods were input as annual rates). Frequency-dependent model is a SEI model with starting dog population of 50,000 and seeded with 2 infectious individuals. Density-dependent model is adapted from Anderson et al. 1981, with starting population density of 15 dogs per km^2 , 0.01 infectious dogs per km^2 , and carrying capacity of 29 dogs per km^2 .*



Supplemental Figure 2. Types of modeling studies. Categories are adapted from Lloyd-Smith et al. 2009: 1) Predict future trends based on currently available data and model projections; 2) Study control measures (using models to estimate/simulate the impacts of control efforts and compare intervention strategies); 3) Estimate key parameters such as R_0 , the incubation period, the dispersal kernel; we also differentiate between studies which 4) Identify drivers of dynamics (that is look at hypothetical factors which may drive transmission without comparing or fitting to data) and studies which 5) Explain observed patterns (use models and data to determine likely drivers of observed patterns).*

Chapter 4

Spatial scale of control and mixing predicts dynamics of canine rabies

4.1 Abstract

Canine rabies is a devastating and preventable disease that causes a high burden of deaths globally each year, particularly in low-and-middle countries where investment in control is limited. Given the mounting evidence that elimination of these deaths is possible, the WHO has set a target to eliminate canine rabies deaths in humans by the year 2030. Mathematical models are a powerful tool to inform these efforts, but to date, efforts to develop robust modeling frameworks for domestic dog populations have been hampered by a lack of data, inconsistencies between model results and observed dynamics. Here, we use a rich, long-term dataset on canine rabies cases in space and time in the Serengeti District in Tanzania. Using parallel data on vaccination campaigns and the underlying spatial distribution of the domestic dog population, we use a simulation-based inference approach to fit our models to key spatiotemporal features of the data. We find that incorporating both the spatial scale of population mixing and the scale of control are key to recovering observed dynamics. We use these results to explore different vaccination scenarios, and find that high spatial coverage of vaccination campaigns is necessary to prevent outbreaks of canine rabies. Moving forward these results provide practical insights into control strategies and modeling methods, as well as shed light on key processes driving rabies transmission.

4.2 Introduction

Rabies is a devastating and fatal disease that causes an estimated 60,000 human deaths annually across the globe (Hampson et al., 2015). However, these deaths are preventable through post-exposure vaccination, which is highly effective at preventing death if administered promptly after exposure, and through vaccination of domestic dogs, which with sufficient coverage can interrupt transmission and lead to elimination (Lankester et al., 2014). Given that the world has the tools to end deaths due to rabies, the World Health Organization and its partners have set a goal to eliminate deaths due to canine-mediated rabies by the year 2030 through a combination of these interventions (Abela-Ridder et al., 2016).

While there is a rich history of modeling wildlife rabies transmission dynamics, the body of work for canine rabies is much sparser. Critically, traditional models of wildlife rabies dynamics fail to capture patterns of incidence observed in endemic and epidemic scenarios. However, we have a strong understanding of rabies epidemiology and biology: transmission does not appear to scale with dog densities evidenced by consistent R_0 estimates between 1 - 2 across a range of settings, the infectious period is short and infection is almost invariably fatal, and that key epidemiological parameters such as the dispersal kernel and the incubation period are characterized by a long tail. While R_0 estimates are consistent and low, there is considerable documented heterogeneity in infection with many infections resulting in no onwards transmission, while some cause upwards of 20 - 50 cases (Rajeev et al., 2020).

While the epidemiological backbone of rabies is clear, there is little data on disease dynamics in domestic dogs with which to confront models (Scott et al., 2017). In fact, most modeling studies of canine rabies are simulation based, with few studies actually fitting models to data (Rajeev et al., 2020). This is largely due to poor surveillance, but given the epidemiological features of rabies combined with low detection rates, inference can be challenging. Rabies outbreaks are highly stochastic and likely driven by heterogeneities and rare events. Therefore traditional inference methods based on times series data are likely to fail when confronted with the noisy reality of rabies data.

Here we use a uniquely comprehensive long-term dataset on canine rabies cases in space and time across the Serengeti District in Tanzania, where ongoing vaccination campaigns have shaped dynamics over the past twenty years. We build on recent work that highlights the role of spatial structure in mixing, simplifying the model, extending it to consider different movement scenarios, and comparing models at the scale of population mixing ($\sim 1 \text{ km}$) vs. at the scale of control (village scale). Coupled with data on vaccination and the spatial distribution of the dog population, we build an individual-based spatially explicit model, and using a simulation-based inference approach, fit it to key spatiotemporal features of the observed data to identify models that best fit our data and gener-

ate realistic dynamics in endemic situations. Finally, we simulate vaccination campaigns and control strategies based on our findings to inform control efforts.

4.3 Methods

4.3.1 Study area

The Serengeti District in Tanzania is approximately 2000 km² in area and is comprised of multi-ethnic agropastoralist communities (estimated human population of 2.49×10^5 at the time of the last census in 2012) with high dog ownership (estimated human-to-dog ratios ranging from 3 to 9). Rabies has been endemically circulating in the district, with documented outbreaks reported as early as the 1950s (Brunker et al., 2015), and rabies vaccination campaigns have been ongoing in the district since the early 1990s. These efforts began as a way to protect wild carnivore communities in the bordering Serengeti National Park, but with research and non-governmental partnerships with the Tanzanian government and vaccine manufacturers, these have expanded into a large scale elimination program.

Since 2002, a long-term study of canine rabies and domestic dogs has been ongoing in the district (Hampson et al., 2009), with data collected on clinical and laboratory diagnosed cases of animal rabies, as well as vaccination and dog ownership data. Here we use three key datasets from this study system:

- 1) Case histories of clinical and laboratory diagnosed dog rabies cases between 2002 - 2020 (N = 3224 observations with approximate date of symptom onset and GPS location (Fig 4.1A and B)).
- 2) Data on village level number of dogs vaccinated annually as part of ongoing district wide vaccination campaigns (Fig 4.1C).
- 3) A full household and dog census of the district conducted between 2009 - 2014, with the spatial location of households, the number of adult dogs and puppies in each household, the number of individuals in these households, and dog vaccination status (Fig 4.1D).

We also used census data on human population sizes from the 2002 and 2012 national census in Tanzania to estimate population growth over the district. Village (i.e. administrative level 3) boundaries for the district were constructed using the distribution of household locations belonging to each village from the dog census data (Fig 4.1D, (et al. in preparation, 2021)).

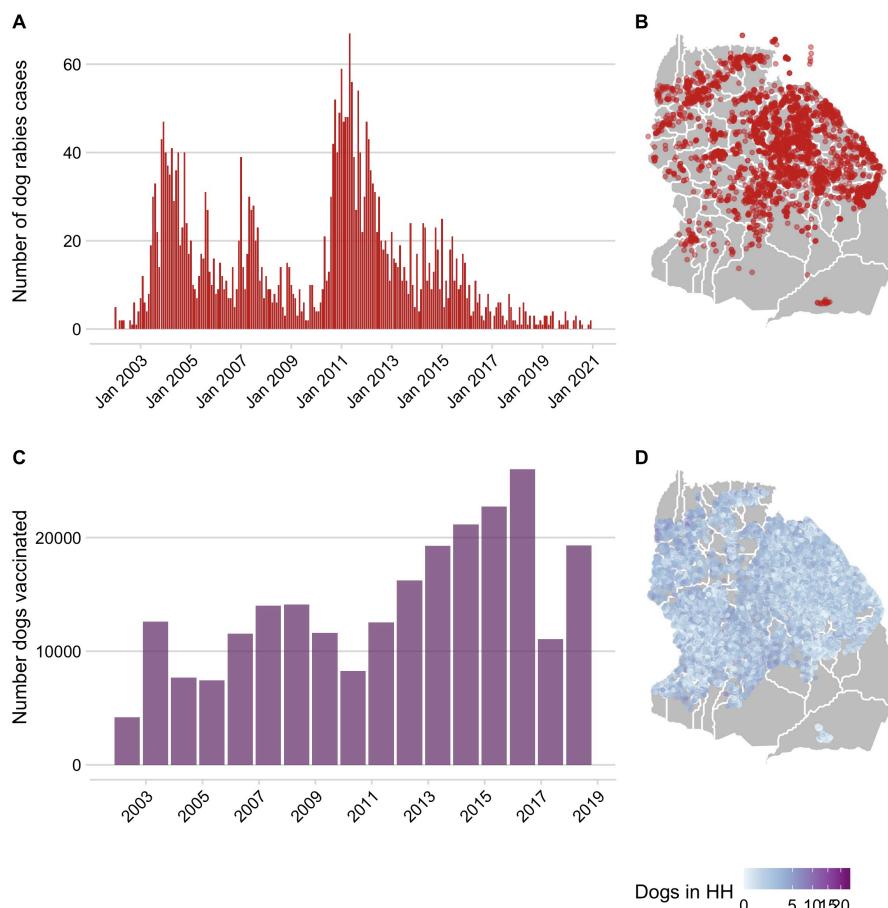


Figure 4.1: Figure 1. Datasets used in the analyses. A) Shows the time series of monthly rabies cases in domestic dogs and B) shows their spatial distribution across the district. C) The annual number of dogs vaccinated each year during mass campaigns. D) The location of household census data with colors showing the number of dogs owned per household. Polygons delineate village boundaries in the district.

4.3.2 A spatially-explicit, individual-based model of rabies transmission

We developed a discrete-time, individual-based, Susceptible-Exposed-Infectious-Vaccinated transmission model to simulate rabies dynamics in the domestic dog population. Transmission occurs at the individual level with secondary cases drawn from a right censored negative binomial distribution with mean R_0 and dispersion parameter k (to capture heterogeneity, but constrained so that secondary cases from a single individual do not exceed 100 cases, a realistic range of transmission potential). Movement of infectious individuals occurs in continuous space, with distances either drawn as a dispersal distance (log normal distribution, i.e. case movements are all drawn in reference to the progenitor location) or as a random walk with a Weibull step length distribution, (i.e. case movements are sequential). The timing of when a dog becomes infectious after exposure is drawn from a lognormal serial interval distribution (the infectious period + the incubation period). Previous work has shown the importance of introductions of rabies cases from outside the district in maintaining transmission within the district (et al. in preparation, 2021). We use two approaches to simulate introductions:

- 1) Using inferred locations of introductions from transmission tree reconstruction between 2002 - 2015 to explicitly seed transmission chains
- 2) Drawing the number of weekly introductions as a poisson distributed variable (ι) and randomly seeding them in space

Demographic processes occur sequentially and are aggregated to the spatial scale being modeled: new dogs are born according to village level birth rates; dogs die at a fixed rate across the district, and finally vaccination occurs. Vaccinations are allocated from the village level to the spatial scale being modeled, allocated by population size in a given location, and we assume that surviving vaccinated dogs are revaccinated in subsequent campaigns, giving a conservative estimate of vaccination. To get initial dog population sizes in each location, we estimate human to dog ratios from the dog census data, and apply them to human population estimates from national census data at the start of our simulation period (2002). We allocate them spatially according to the distribution of households and dogs from the census data. To get village level growth rates, we estimate human population growth between 2002 - 2012 from the national census data at the village level and assume that dog populations grow at that same rate (and assume a fixed death rate, Table 1, Czupryna). We do not apply demographic transitions to exposed or infectious individuals (i.e. they only move out of their classes when moving from exposed to infectious or infectious to removed).

We use a weekly time step to aggregate both demographic and transmission events (i.e. infectious dogs in location x at week t all compete for the same contacts) and explore different scales of spatial mixing: at an 1 km^2 resolution and at the village scale (in UTM Zone 36S such that distances between

grid cells are as close to 1 km as possible). Fig ?? lists all parameters and their sources. In addition to comparing mixing at the village and 1 km scales, we also explore how further constraining movement of rabid dogs impacts model inference. At the baseline, we do not constrain movements of rabid dogs: that is rabid dog movements to locations outside of the district or to uninhabited patches will result in a failed transmission event. We compare this baseline (which we refer to hereafter as the no limits model) with a model that restrict movements to only inhabited patches (i.e. populated patches at the beginning of the simulation, the patch limits model), and finally a model that restricts movement to both uninhabited patches and to the district (the full limits model). For the constrained models, we do not resample individual movements that fail as this could potentially skew the underlying parameter distance distribution (for example, if resampling happens often enough, this can shift both the average and skew of the distribution). Instead, for each movement we draw distances, find grid cells within that distance, and sample movement to valid locations given the model constraints. We assume that infection is completely fatal, and infectious individuals are removed at the end of the weekly timestep during which they became infectious. Finally, to account for imperfect case detection we use a monthly beta binomial detection probability (??).

Input (units)	Distribution
Secondary case distribution (number of dogs)	Right censored negative binomial distribution with mean = \$R_{\{0\}}\$
Weekly rate of introductions	Poisson distribution
Serial interval distribution (days)	Lognormal distribution with mean = 2.95, and sd = 0.86
Dispersal kernel (meters)	Lognormal distribution with mean = 5.58, and sd = 1.79
Step length distribution (meters)	Convolved Weibull distribution with shape = 0.39, and scale = 58.29
Annual death rate (dogs/yr)	1/25.8 yrs
Rate of waning vaccine immunity (dogs/yr)	1/3 yrs

4.3.3 Model selection & parameter estimation

We use Random Forest Approximate Bayesian Computation (RF-ABC) implemented in the R package **abcrf** (Pudlo et al., 2015; Raynal et al., 2018) to perform model selection and parameter inference. We estimate three parameters: R_0 (the mean of the secondary case distribution), k (the dispersion parameter of the secondary case distribution), and ι (the mean weekly number of introductions of rabies cases from outside of the district). We use strong priors based on previous analyses of part of this dataset (Fig ??)(Hampson et al., 2009). RF-ABC can be used to evaluate both models and potential summary statistics (i.e. key features of the data that the model should capture). Fig ?? lists the candidate summary statistics we used for model selection and parameter estimation, encompassing temporal, spatial, and spatiotemporal metrics of the data. RF ABC ranks each of these parameters

by their importance in predicting a given parameter or in differentiating models. For both model selection and parameter estimation, we generate $N = 1e5$ simulated sets of summary statistics. We use the default parameter of 500 trees in the random forest for estimation, and also perform a sensitivity analysis with subsets of the full dataset (subsampling to 75% of simulated dataset) to assess whether estimates are stable. We use out-of-bag error rates (the error rate of the out-of-bag classifier on the training set) for model selection to assess the stability of model estimates to the number of simulated datasets and the number of trees in the Random Forest (Raynal et al., 2018). RF-ABC does not allow for joint parameter estimation, however, we approximate joint posteriors by including parameter sets where all estimated parameters were accepted (i.e. all values were assigned non-zero weights by the random forest classification).

We perform model selection for models within spatial scales, i.e. to identify the best candidate model at the village and 1 km scale. We then simulate from the estimated posterior distributions ($N = 1000$) and compare this to our observed data. We score simulations using the continuous ranked probability score (Jordan et al., 2019), and for each simulation of the monthly time series, we also generate centrality scores (i.e. how representative is a given simulation of the ensemble, (Juul et al., 2020)) and also the root mean squared error (RMSE) against the observed monthly cases. We also simulate an endemic scenario with no vaccination to see if the models can generate realistic dynamics in this context.

Summary statistic	Description
Max I	Maximum monthly number of cases
Median I	Maximum monthly number of cases
Mean I	Mean monthly number of cases
Temporal KB	Kullback-Leibler Divergence between observed and simulated distribution of cases over time
Spatial KB	Kullback-Leibler Divergence between observed and simulated distribution of cases across space
Mean distance 4 weeks	Mean distance between cases within an 4 week window
Mean distance 8 weeks	Mean distance between cases within an 8 week window
Mean distance 4 weeks normalized	Mean distances of cases within an 4 week window, normalized by the average mean distance
Mean distance 8 weeks normalized	Mean distances of cases within an 8 week window, normalized by the average mean distance
Spatial RMSE	Root mean squared error between the observed vs. simulated density of cases across space
Spatial loss	Loss value of the absolute difference between observed and simulated cases across space
Temporal RMSE	Root mean squared error between the observed vs. simulated numbers of cases over time
Temporal loss	Loss value of the absolute difference between observed and simulated monthly incidence
Mean distance all cases	Average distance between all cases
ACF Monthly 1-6	Autocorrelation values for monthly timeseries at 1 - 6 month lag
ACF Weekly 1-10	Autocorrelation values for weekly timeseries at 1 - 10 week lag

4.3.4 Assessing simulated vaccination campaigns impact on transmission

To explore how spatial heterogeneities in vaccination coverage could drive outbreak risk, using our best model, we simulate across a range of campaign scenarios. We vary both the level of coverage achieved during annual campaigns (campaign coverage), and the proportion of villages which are vaccinated during campaigns (spatial coverage), and use our posterior estimates to simulate transmission dynamics. We simulate these campaigns ($N = 100$ simulations per combination) with random villages being vaccinated with probability x in each year. We simulate a five year endemic burn-in period, and then simulate annual campaigns over ten years. In the last five year period of the simulation, we calculate summary statistics that capture key metrics of control success such as peak and mean incidence, chain size and length, and weeks where transmission exceeds the 95th% of the mean incidence of introduced cases only. We also calculate a connectivity based summary statistic at the village level (c) which equals the sum of squares of the component size of the village graph, where villages are connected if they are adjacent and if coverage at that time step exceeds a threshold (the campaign coverage for a given simulation).

4.3.5 Assessing the impact of additional interventions on transmission and outbreak probabilities.

We also explore approximations of different intervention strategies implemented in tandem with vaccination on outcomes using our best model. We simulate approximations of two different interventions in combination with the random village campaigns as described above: 1) ‘Chopping the tail’ of the secondary case distribution, where we decrease the censoring value as vaccination increases, to approximate how enhanced surveillance and isolation/quarantine/removal of rabid dogs can improve control outcomes 2) Reducing introductions as coverage increases, i.e. approximating coordination of vaccination campaigns across larger spatial scales

(Fig S??) shows the reductions in introduction rates and maximum allowed secondary cases given district level coverage.

4.3.6 Data and ethics statement

The data used in these analyses are part of a long term research project in the Serengeti District approved through the University of Glasgow Ethics Board and by the Tanzania Commission for Science and Technology, and National Institute for Medical Research. Anonymized data and code are available at gitub.com/mrajeev08/dynamicSD (to be archived on zenodo and made public upon article submission) and the underlying simulation model is available here (github.com/mrajeev08/simrabid). All analyses were done using R [cite] and the following key packages: abcrf, ranger, data.table, sf, raster.

4.4 Results

4.4.1 The scale of mixing and specification of introductions differentiate models.

Parameter estimates and model predictions largely varied across two axes: whether introductions were estimated or fixed within the model and the scale of mixing (a 1km² scale vs. the village scale). The models with kernel based movement and estimating introductions were both ranked highest for both scales, and at the 1 km scale, models that further restricted movement to inhabited patches (patch limits model) was best predicted the data (Fig S4.7). Summary statistics that best differentiated the models encompassed both spatial and temporal summary statistics, and the linear-discriminant analysis axes generated by the RF ABC model (Fig 4.2B). These results were robust

to subsampling the datasets (Fig S4.9) and out-of-bag prior error rates were relatively stable with inclusion of additional trees in the random forest model (Fig S4.10). (Fig ??B. However, broadly, all the models and priors failed to consistently recapture the major components of the summary statistics (Fig 4.2A) or clearly differentiate between models within scales (Fig S4.8).

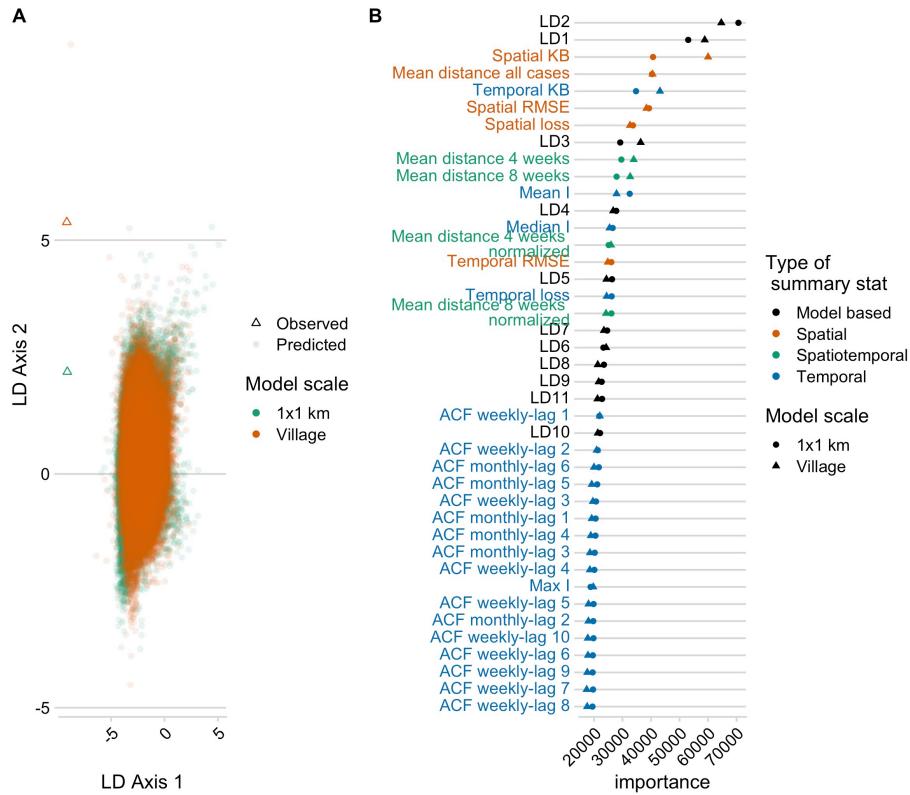


Figure 4.2: Model selection using RF ABC. A) The two major LDA axes generated by the random forest model for the best model at the village and 1 km scale, with the LDA values predicted for the observed data shown as triangles. B) The importance ranking of each variable in discriminating between models.

4.4.2 Capturing the spatial scale of vaccination and of mixing is key to recovering the observed trajectory of rabies in the Serengeti District.

We estimated three parameters: R_0 , k , and ι (for models estimating introductions) using these same models and summary statistics. R_0 was best predicted by temporal summary statistics, while k and ι were predicted by spatial and spatiotemporal summary statistics (Fig 4.3, Fig S4.11). Estimates of R_0 were consistent and identifiable across the models and robust to subsampling simulations (Fig S4.13, but varied significantly across scales and introduction scenarios (Fig S4.12. When comparing posterior estimates for the best models at each scale, R_0 estimates were lower in models at the village scale when compared to the 1 km scale (Fig 4.4, 4.4.2). Estimates of k and ι were more diffuse, and when filtering to parameter sets that had been accepted jointly (i.e. had non-zero weights for all three

parameters), estimates of the introduction rate became sharper, while k became bimodal (Fig S4.12).

\begin{table}

\caption{Independent posterior expectations (and 95\% quantile) estimates for the best model at each scale.}

Scale	\$R_{\{0\}}	\$k\$	\$\backslash iota\$
1x1 km	1.11 (0.97 - 1.24)	3.35 (0.79 - 8.7)	1.75 (0.8 - 3.93)
Village	1.02 (0.89 - 1.15)	3.02 (0.94 - 7.36)	1.89 (0.98 - 4.68)

\end{table}

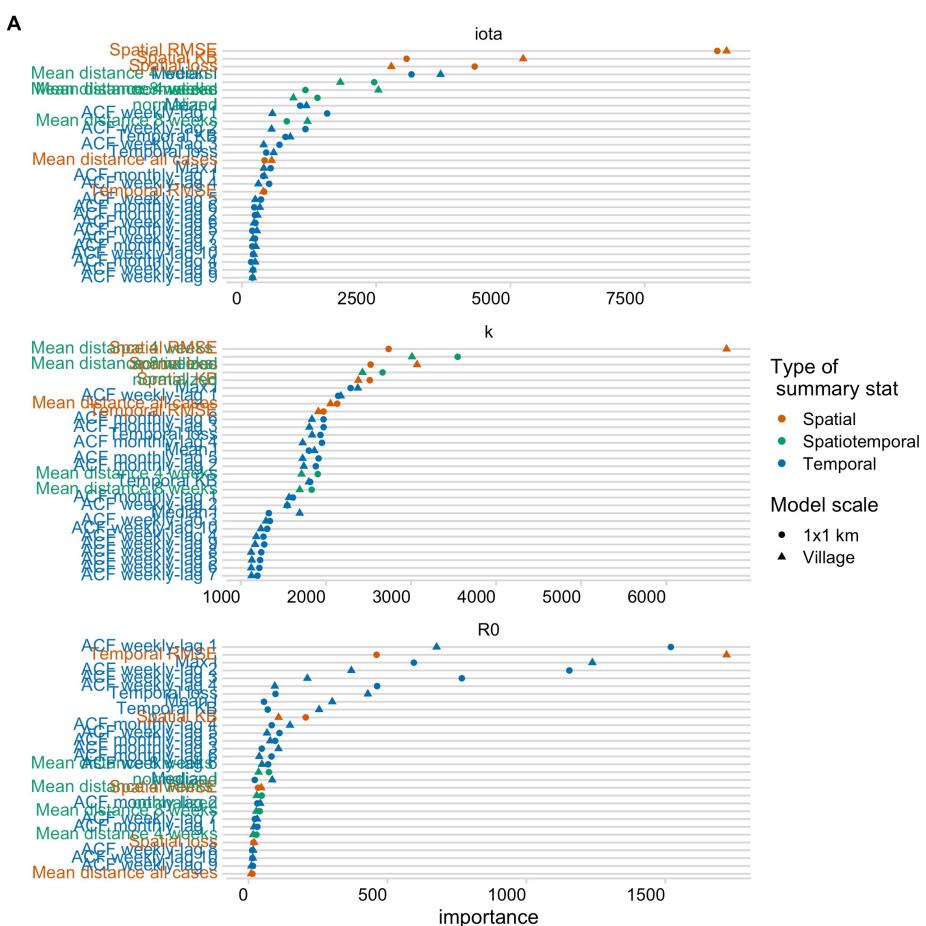


Figure 4.3: Ranking of summary statistics for importance in predicting each parameter. Summary statistics are colored by the type of statistic (either spatial, temporal, or spatial temporal). Results are shown for the best fitting model at the village and 1 km scale.

When simulating the data from the posteriors, the models ranked highest by the RF ABC method estimates result in simulations closest to the data observed (??, Fig S??). Sampling from the joint parameter sets also improved fits to the data (Fig S??, Fig S??). At both the village and 1 km scale, simulations encompass the trajectory of cases we observed. However, the village scale model fails to capture stable dynamics in an endemic scenario with no vaccination, with transmission

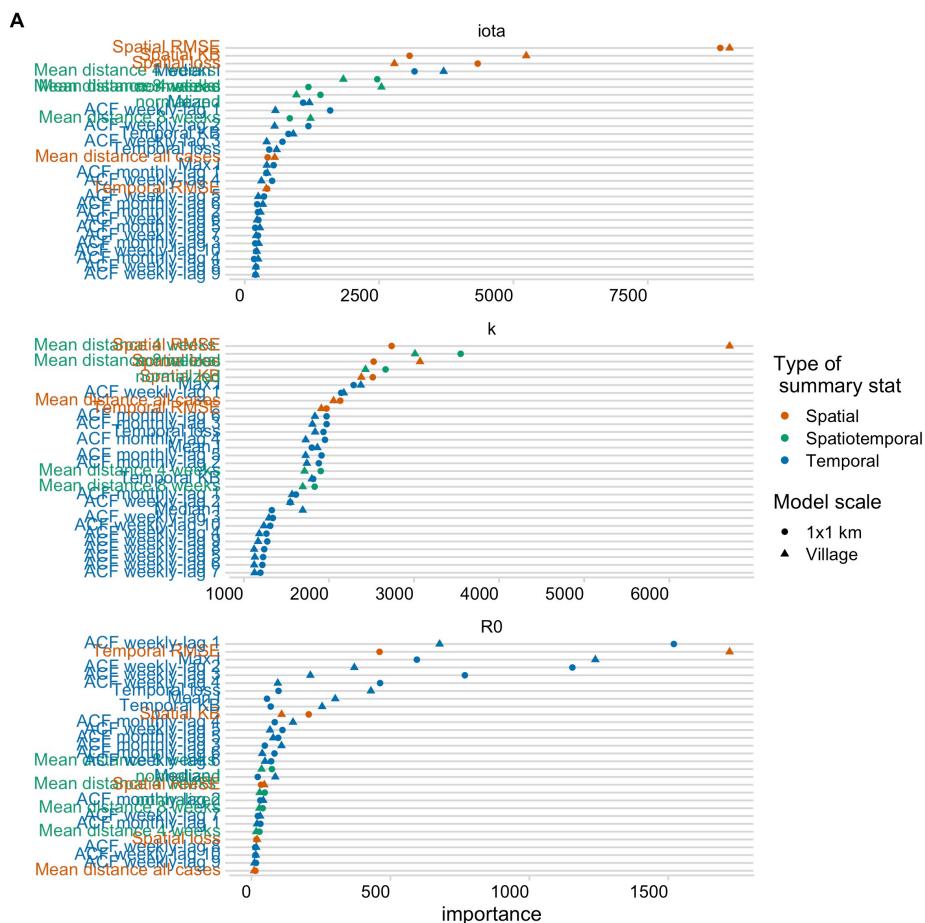


Figure 4.4: Independent and joint posterior estimates for the best fitting model at the village and 1 km scale for the three parameters, with prior density in grey.

resulting in significant declines in the host population, while models at the 1km scale generate stable endemic incidence without depleting the host population (Fig S??).

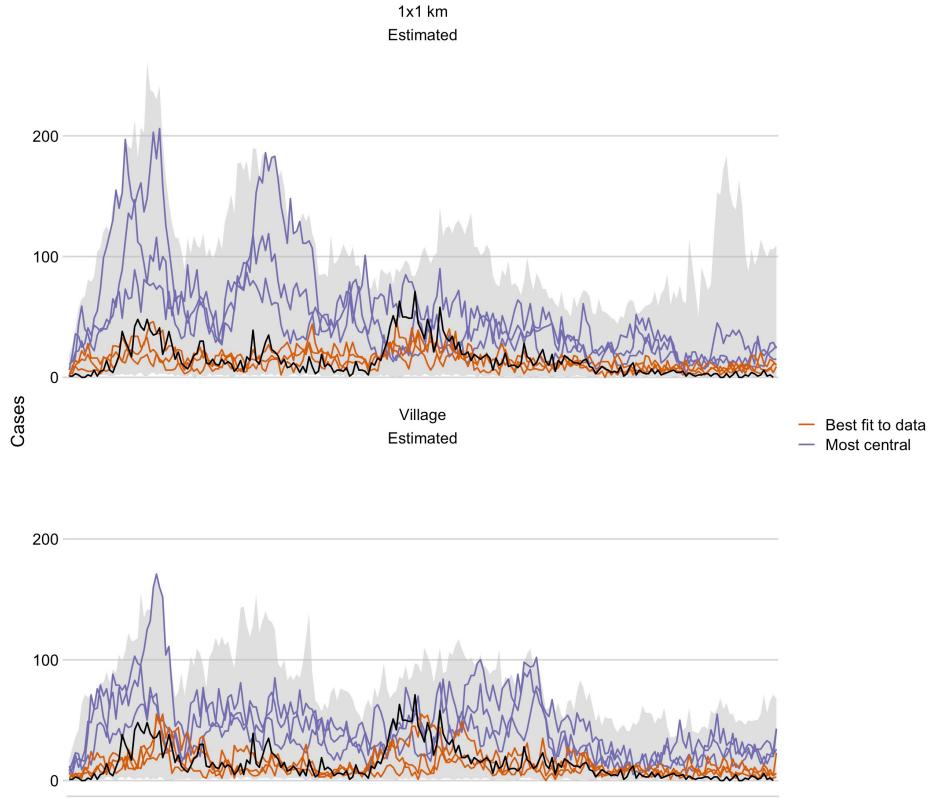


Figure 4.5: Simulations from the joint posterior distributions of the best fitting model. The grey envelope shows the range of simulations, and the black line is the time series of observed monthly cases. The orange lines show the top three simulations that best fit the data (lowest RMSE) and the purple lines show the top three simulations that have the highest centrality score.

4.4.3 Spatial coverage of vaccination predicts control outcomes and interventions that target key features of transmission improve these outcomes.

We find that control outcomes are strongly predicted by both campaign (i.e. the coverage level achieved by a village campaign) and spatial coverage (the proportion of villages covered by a campaign)(Fig S??). We find that campaigns that achieve an annual campaign coverage of 80% of the population and a spatial coverage of 80% of villages are most likely to prevent outbreaks of canine rabies (defined as greater than 4 months with weekly cases greater than the 95% of the average of the introduced cases) (??). These broadly track with other metrics of control outcomes as well, such as the average peak size and length of transmission chains, and mean and peak incidence (Fig S??). In general, both spatial and campaign coverage are more predictive of peak rather than average metrics (Fig Fig S??). Connectivity of vaccinated villages varies the most at

intermediate spatial coverage, and this metric also broadly predicts control outcomes within a given campaign scenario (Fig S??).

Two additional control strategies, one increasingly censoring transmission as coverage increases, approximating control strategies such as tracing and quarantine, and the second reducing the introduction rate as coverage is increased, approximating coordinated control efforts across larger geographic scales, also greatly improve control outcomes (Fig S?? and Fig S??). In particular, reducing the introduction rate shifts both the spatial coverage and campaign coverage required to limit outbreaks (??).

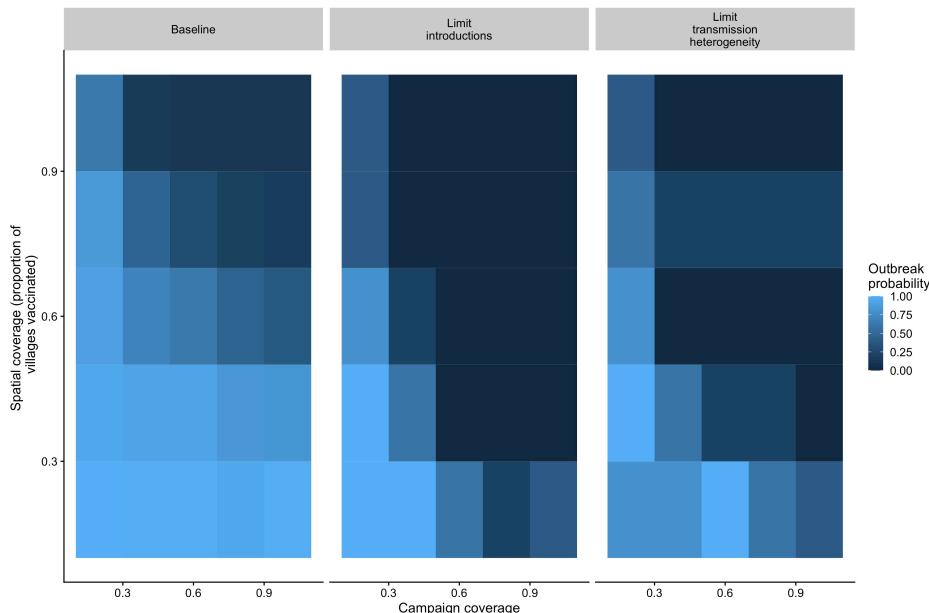


Figure 4.6: Outbreak probabilities (defined here as whether the number of consecutive weeks with cases above the 95th% of the incursion rate exceeding 16 weeks) in relation to a range of campaign coverage and spatial coverage under the baseline scenario and with the additional limits on transmission heterogeneity and introductions.

4.5 Discussion

Overall, we find that accounting for both the spatial scale of vaccination and of mixing is critical to capturing the observed dynamics of canine rabies in the Serengeti District. Confirming previous work, we show that modeling transmission at the scale of dispersal ($\sim 1\text{km}$) is key to capturing stable endemic dynamics and also result in parameter estimates closest to empirical estimates from individual scale data. We also found that introductions of cases from outside the district are crucial to the maintenance of transmission. Importantly, spatial and spatiotempral features of the data were key to differentiating between models and identifying parameter estimates, and the time series statistics of the data were generally the least predictive of model separation or parameter estimates.

We find that high spatial coverage of vaccination campaigns is key to predicting control outcomes, even at a coarse administrative level. Aiming for vaccination targets that account for spatial as well as annual temporal targets (i.e. 70% of dogs in at least 70% of villages) rather than a single coverage target may improve control outcomes. In addition, given the importance of transmission heterogeneity and introductions in transmission, control measures targeted at these key features, i.e. reducing superspreading and curtailing transmission through active surveillance approaches, as well as coordinating control across larger geographic scales as vaccination campaigns are implemented, could compound the dividends gained through vaccination alone.

We use a uniquely comprehensive data set in both temporal and spatial scope in our analysis. This data allow us to pin down key features and expectations of rabies transmission, and the vaccination and population data provide a lens into the underlying susceptible dynamics of the population. In addition, we have a strong empirical understanding of key epidemiological parameters governing rabies transmission (i.e. incubation and infectious periods, dispersal kernels). Regardless of working with strong priors and in a narrow parameter space, certain parameters were still not identifiable and no model was consistently able to predict the data observed. Further refining summary statistics that draw the most information out of the available data or using may be a way forward to deal with these identifiability issues. However, given the stochastic nature of transmission dynamics focusing on whether the observed data falls in the general trajectory space of the model may be the best we can do. The RF-ABC method is limited to estimation of independent parameter estimates, and we use a simple approach of filtering parameter sets where all weights are non-zero to approximate joint distributions. However, more work is needed to validate this approach, and improvement of the model computational approach to adapt it to sequential MCMC approaches.

There are also uncertainties in the data that we did not account for. We use coarse demographic estimates at the village scale to simulate populations and do not account for immigration, emigration, or colonization of new patches. Our coverage estimates could be sensitive to these assumptions, although at the village scale, they generally track with estimates of vaccination coverage from post-vaccination surveys. In addition, we do not account for uncertainty in the case data in terms of timing and location of cases, and we use data on probable rabies cases rather than confirmed, but this approach has been shown to be highly specific in identifying true rabies cases (Hampson et al., 2009). We assume that case detection is high over this period, with approximately 85% of cases detected each month. More work is needed to assess how sensitive our parameter estimates and model choice are to detection scenarios. Finally, our simulated control and vaccination scenarios are phenomenological and simplified approximations, rather than explicit representations of control programmes.

Overall, we excluded many features of previous rabies modeling studies. We simulate secondary cases rather than biting rates and exposure probabilities (et al. in preparation, 2021), we do not account for human mediated dog movement within the district (Ferguson et al., 2015; Townsend et al., 2013), we do not model the wildlife population (Fitzpatrick et al., 2012), and finally we do not include reactive control to rabies outbreaks (Ferguson et al., 2015; Townsend et al., 2013). However, many of these features are likely captured implicitly within this model. Human-mediated dog movements and wildlife cases may be captured in the introduction rate, and reactive control (that is not based on increasing response with incidence) is likely captured in the dispersion parameter (i.e. tying/killing/isolation of dogs resulting in failed transmission events). Here, we show that including these features explicitly may not be necessary when modeling transmission at the appropriate spatial scale and when incorporating key epidemiological features of the data (i.e. transmission heterogeneity). However more work will be needed to distentangle these factors, particularly in identifying the role of introductions in transmission. Reactive contol in particular, has often been used as a mechanism in previous models to generate realistic endemic dynamics and prevent host population declines, however there is little evidence that these measures scale temporally with incidence (Hampson et al., 2009). As the village level model did result in simulated trajectories matching our observed data, modeling dynamics at the scale of the control intervention may be sufficient to capture dynamics, and metapopulation models at the scale of control that approximate mixing could greatly reduce data barriers to implementing spatial models (i.e. estimating the underlying population at a high resolution)(Pascual et al., 2011).

This work broadly confirms previous work on canine rabies tranmission dynamics showing the importance of coverage heterogeneity in determining control outcomes and the spatial scale of mixing (et al. in preparation, 2021). Recent phylodynamic analyses of integrated sequence and epidemiological data have also highlighted the role of introductions from surrounding populations (Zinsstag et al., 2017; Bourhy et al., 2016; Laager et al., 2019). These studies were largely at the scale of urban cities, and the authors argue that this indicates that rabies is not maintained within the population being studied. We find similar results in the Serengeti context, a less densely populated mosaic of agropastoralist communities. Together this work suggests that maintenance for canine rabies likely occurs across large spatial scales (Hampson et al., 2007), and that low frequency events such as long-tailed disease induced dispersal or human mediated dog movement could facilitate this (Brunker et al., 2015; Talbi et al., 2010). This has significant implications for control in that there are unlikely to be key sources or sink populations, or a critical community size for persistence (ide, 2002). Rather, as phylogenetic analyses of cases from this district show, there are likely critical landscape structures over which rabies can persist (Brunker et al., 2018).

Broadly, these results indicate the need to integrate key epidemiological features of transmission into

dynamic models. We show that many aspects of transmission that have been included in previous models can be incorporated implicitly, and that modeling both the spatial scale of control and transmission is important for capturing observed dynamics under vaccination and stable endemic dynamics. Practically, developing spatial control targets may be a useful approach to improving the link between targets and outcomes, and providing improved guidelines for vaccine implementation.

However, more work should be done on how landscape and community structure impacts these outcomes. Moving forward, our work highlights the importance of confronting models with data and of incorporating key epidemiological features into models to generate realistic endemic and epidemic dynamics.

Supplementary Figures for Chapter 4

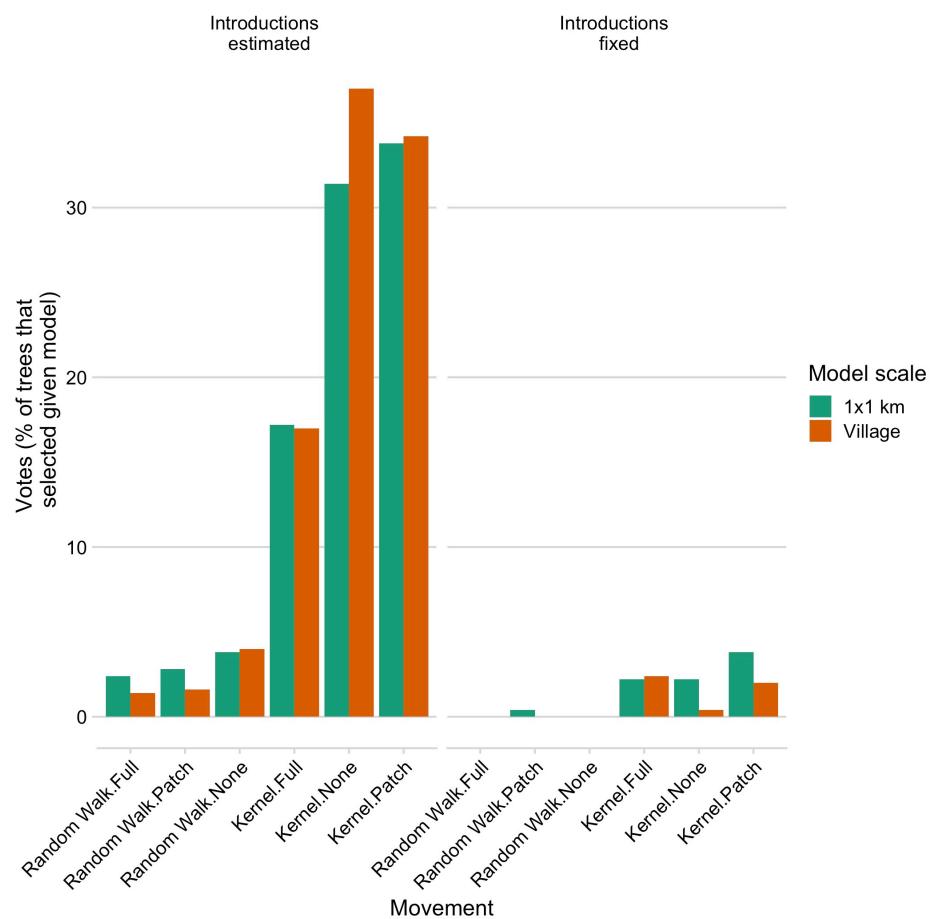


Figure 4.7: Percent of times each model selected with the panels comparing models with fixed vs. estimated introductions, the colors showing the model scale, and the x-axis how movement was specified (see Methods).

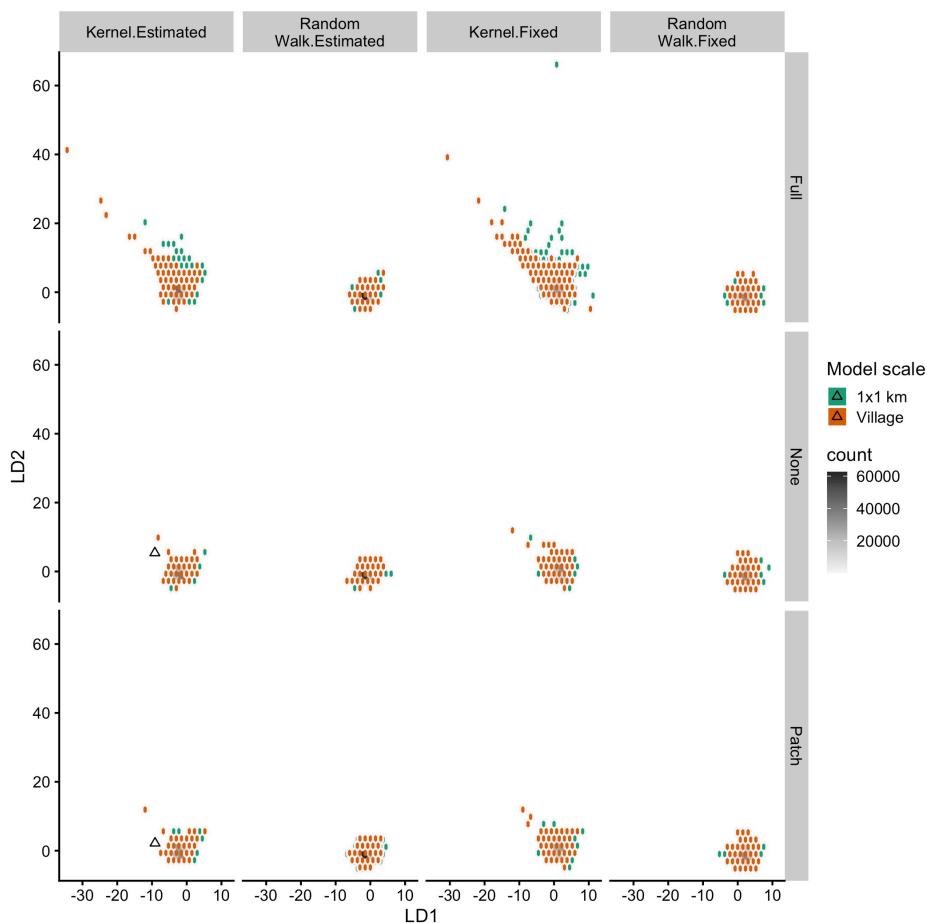


Figure 4.8: Predictions for observed vs. simulated data along the two major LDA Axes for all models. Colors indicate the scale of model, the columns are the type of movement and whether introductions were estimated or fixed, and the rows indicate how movement was restricted (see Methods).

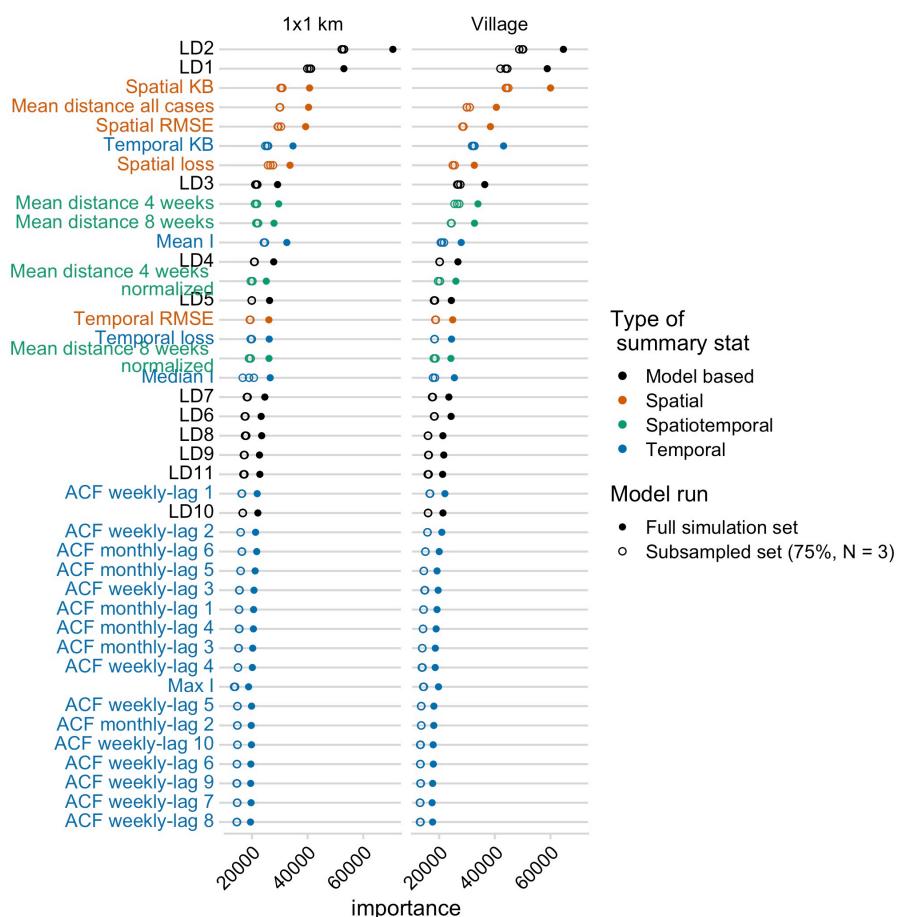


Figure 4.9: Variable importance plots for models run with the full simulation data set ($N = 1e5$ simulations per model), or subsampled datasets (approx. 75% of the full simulation data set).

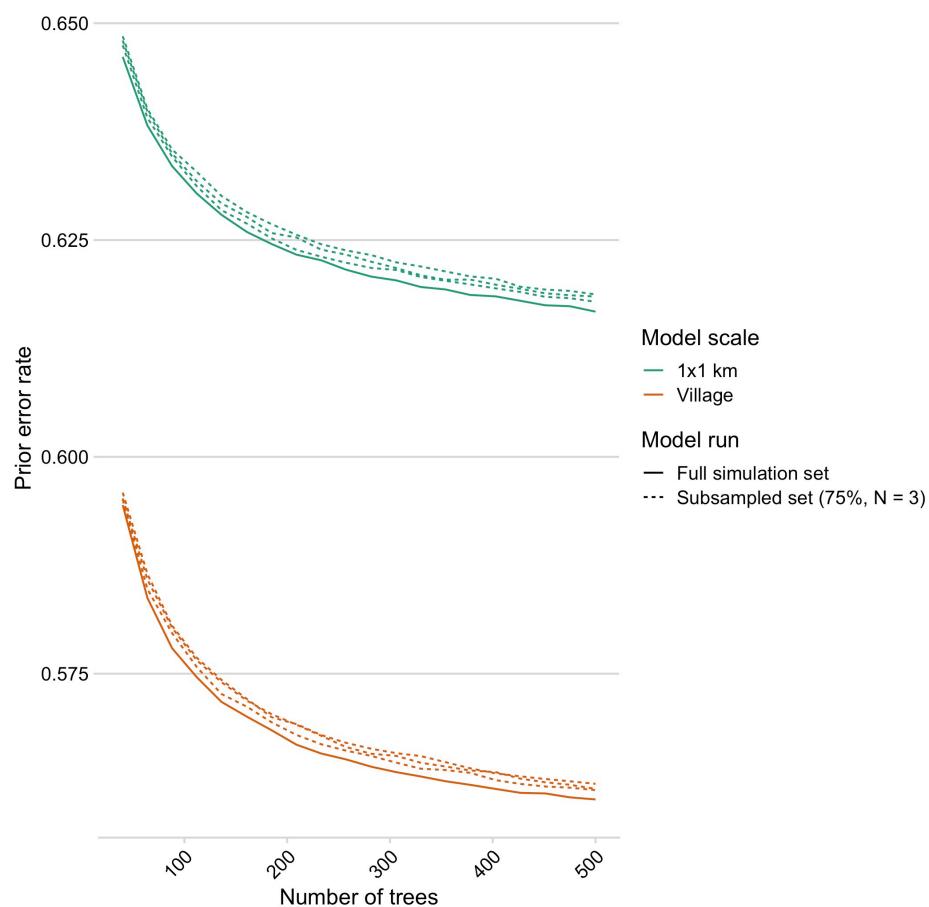


Figure 4.10: Out-of-bag predictions of the out-of-bag error rate as trees are added separated by the scale of the model comparison.

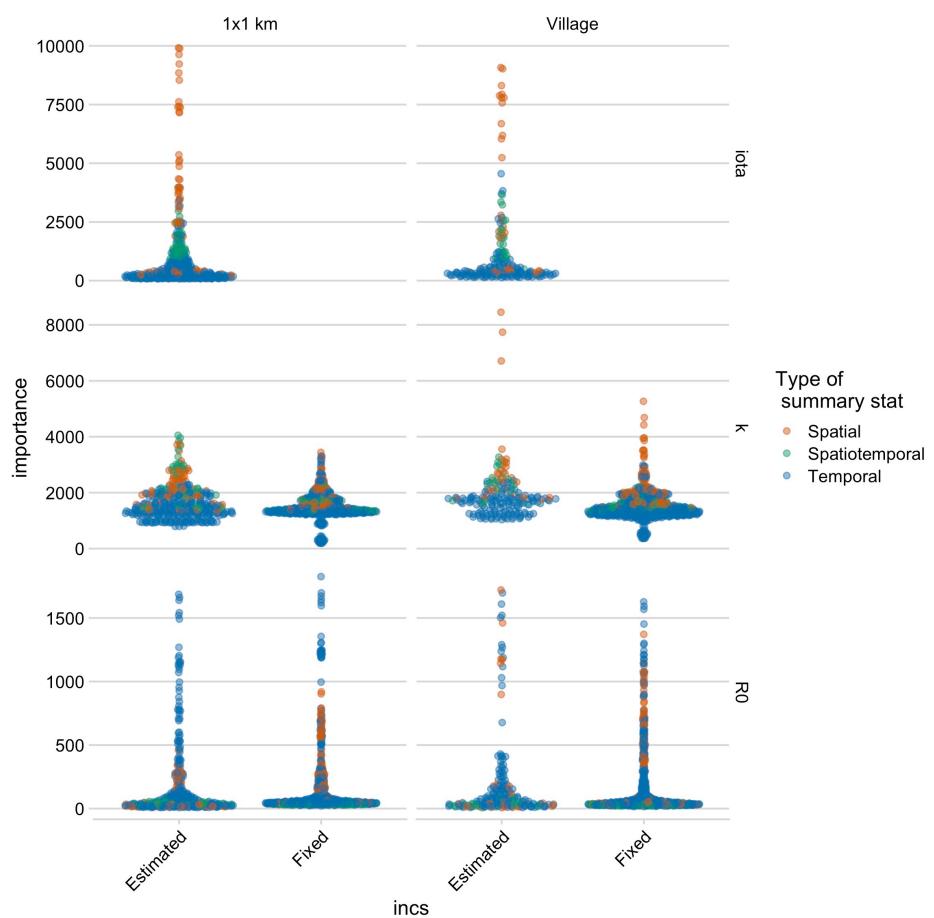


Figure 4.11: Variable importance plots for models run with the full simulation data set ($N = 1e5$ simulations per model), or subsampled datasets (approx. 75% of the full simulation data set) for each parameter and model.

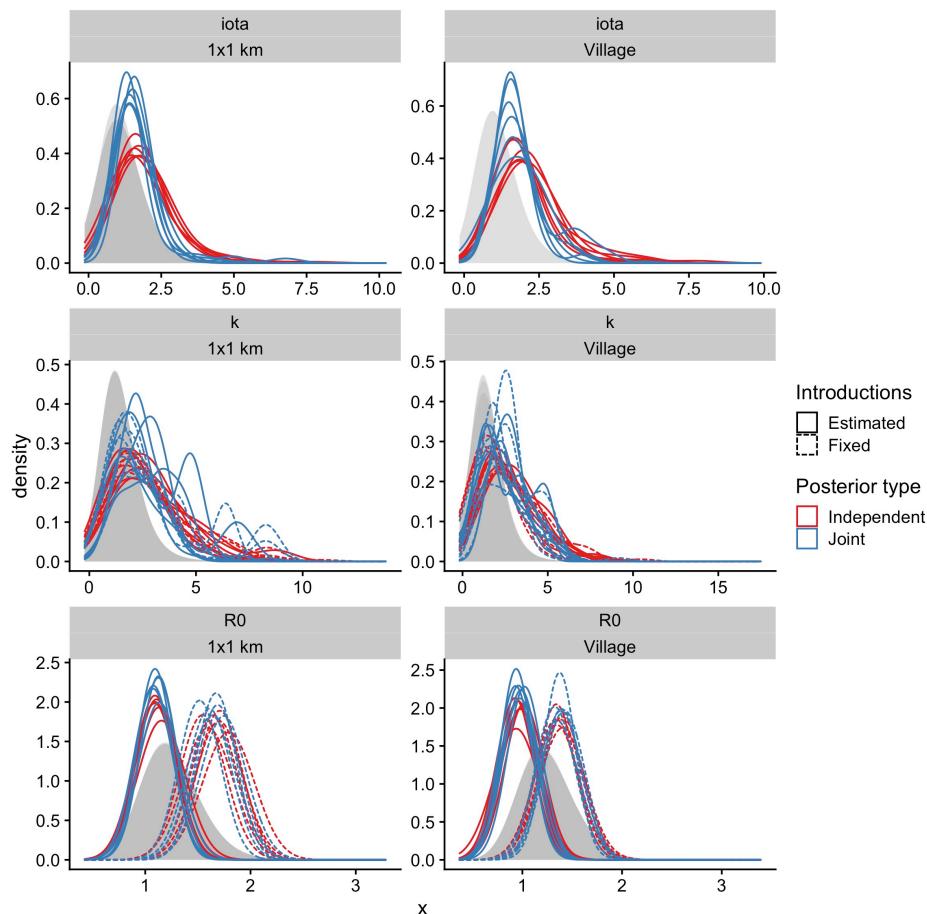


Figure 4.12: Independent posterior estimates for models run with the full simulation data set ($N = 1e5$ simulations per model), or subsampled datasets (approx. 75% of the full simulation data set) for each parameter and model

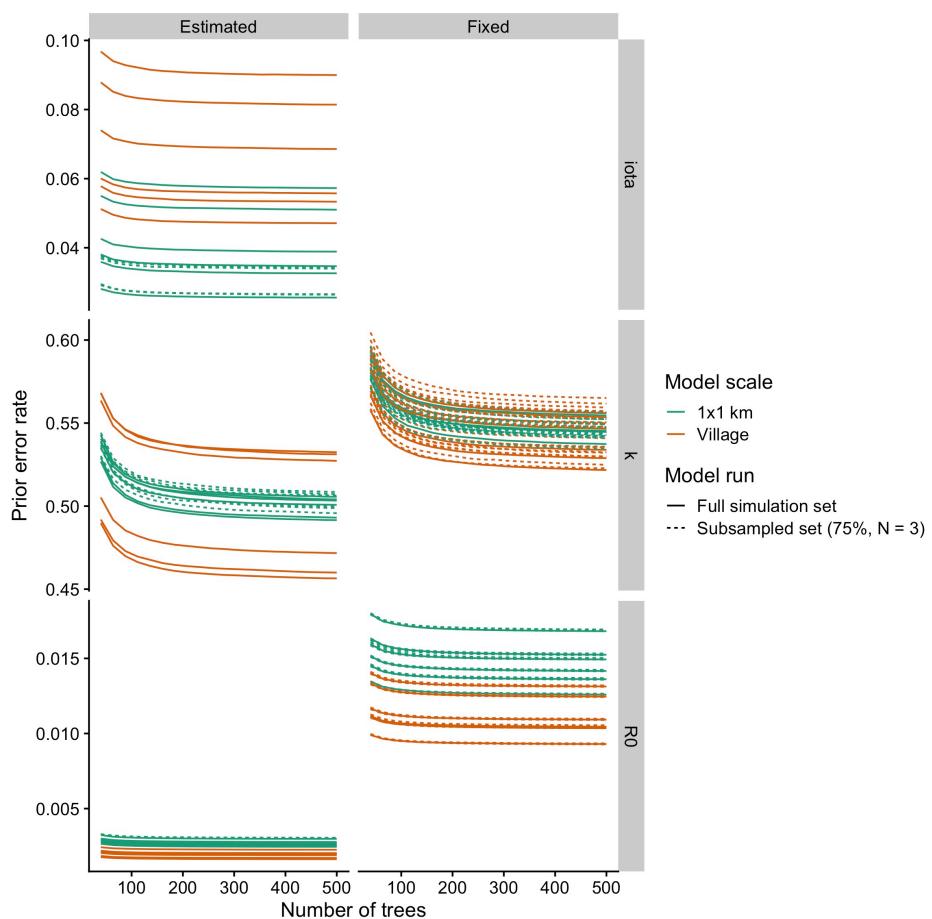


Figure 4.13: Out-of-bag error rates as trees are added separated by the scale of the model comparison and the parameter being estimated.

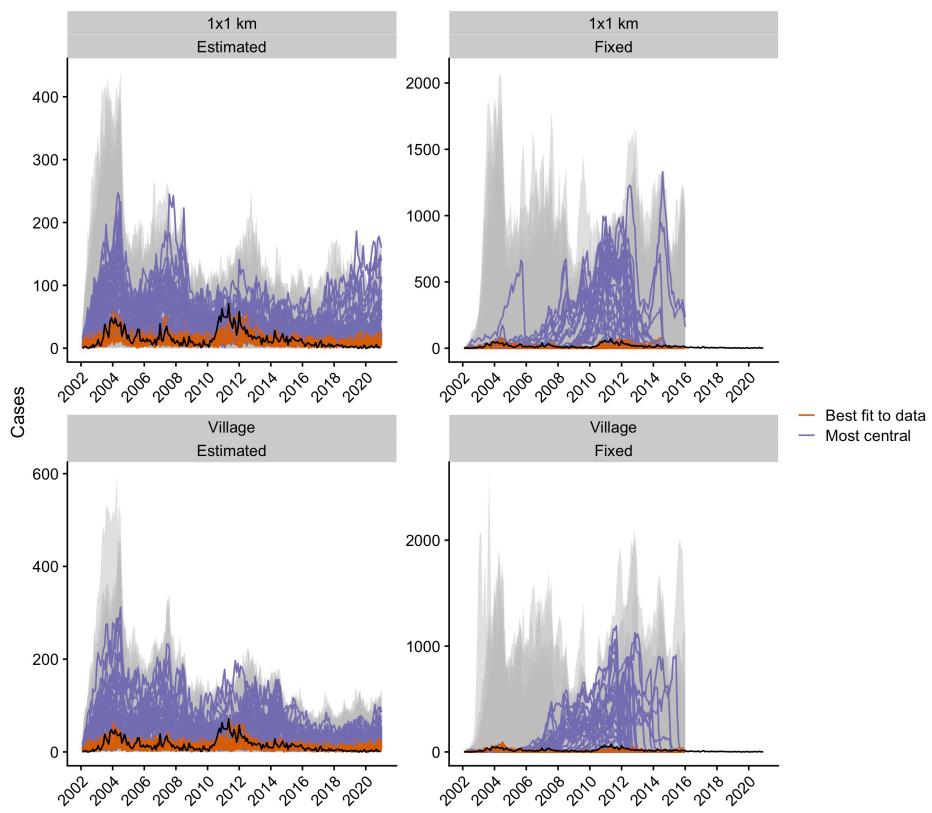


Figure 4.14: Simulations from the independent posterior estimates for all the models. The grey envelope shows the range of simulations, and the black line is the time series of observed monthly cases. The orange lines show the top three simulations that best fit the data (lowest RMSE) and the purple lines show the top three simulations that have the highest centrality score.

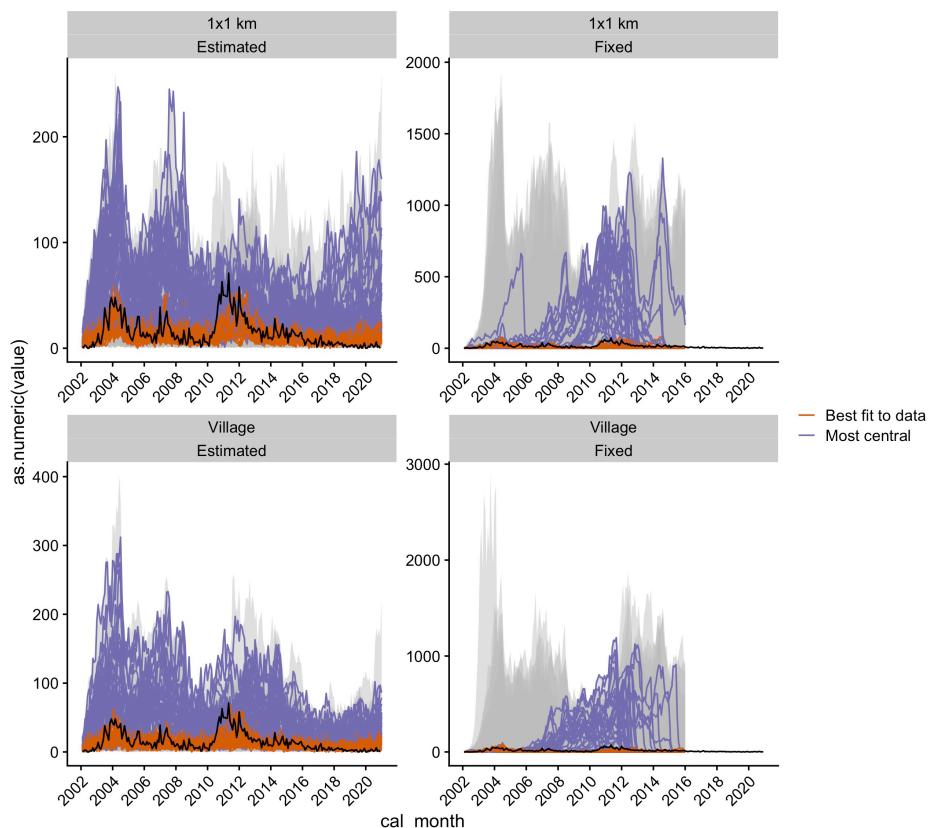


Figure 4.15: Simulations from the joint posterior estimates for all the models. The grey envelope shows the range of simulations, and the black line is the time series of observed monthly cases. The orange lines show the top three simulations that best fit the data (lowest RMSE) and the purple lines show the top three simulations that have the highest centrality score.

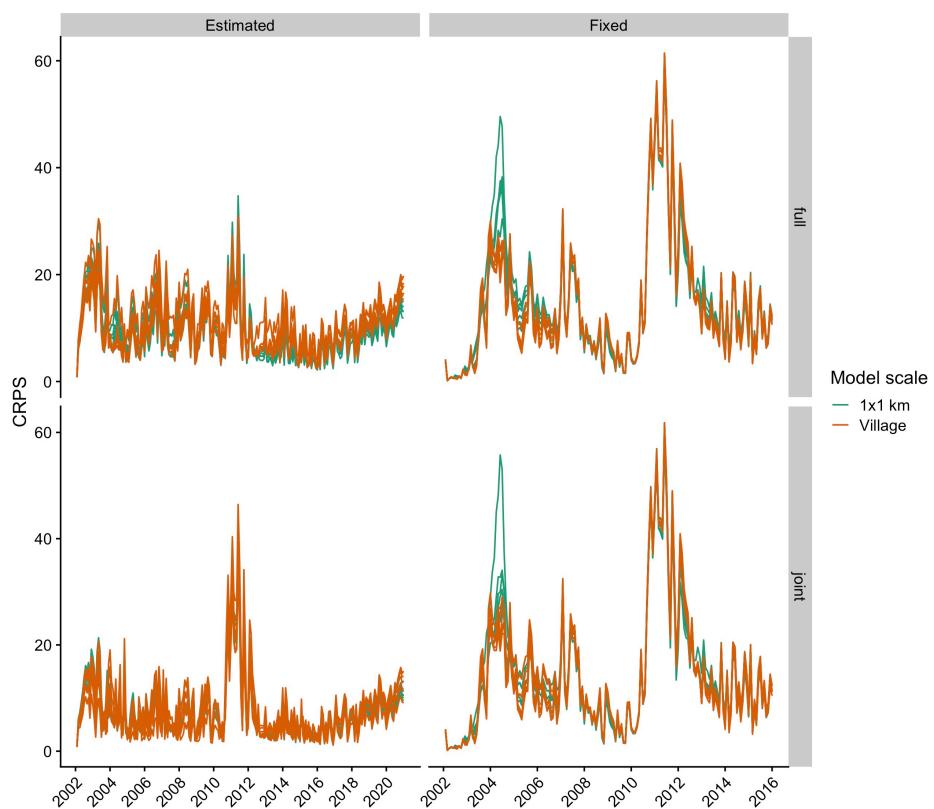


Figure 4.16: Continuous ranked probability scores for the simulated datasets compared to the observed.

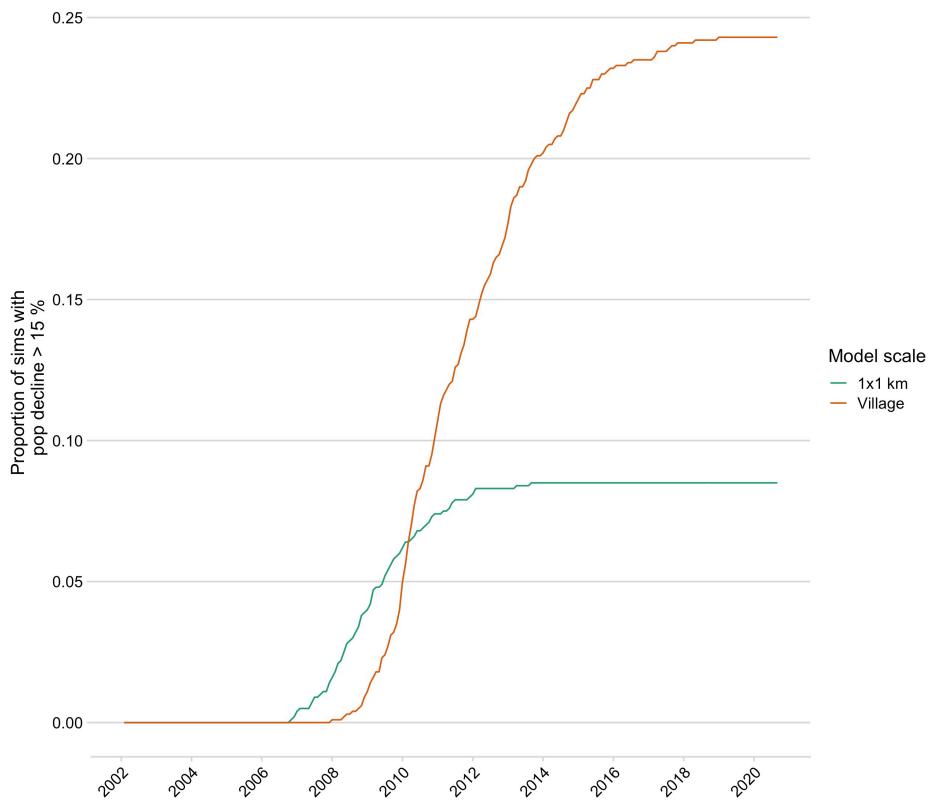


Figure 4.17: The proportion of simulations resulting in population declines $> 15\%$ by each time step for the best model at each scale.

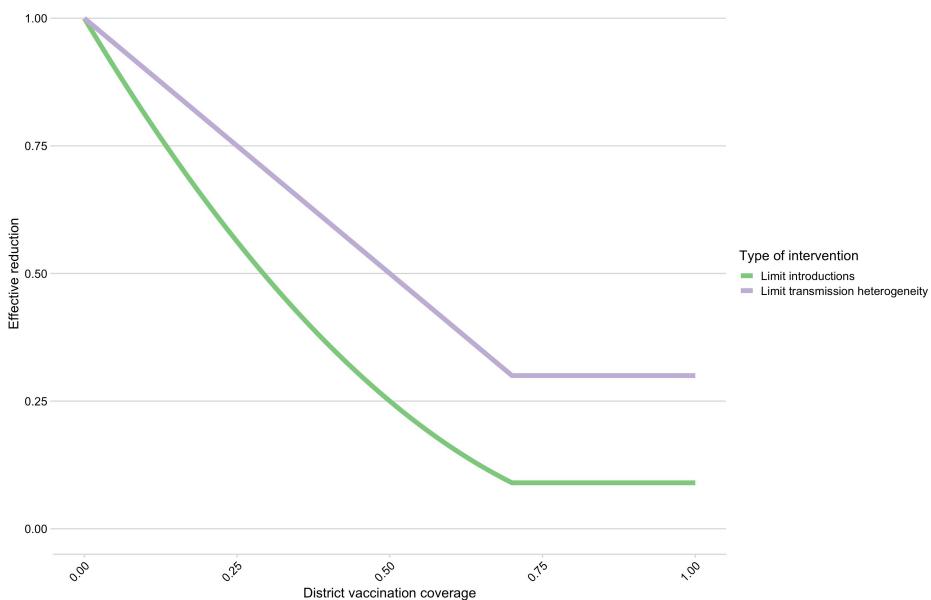


Figure 4.18: The relationship between district level proportion susceptible and reduction in introduction rate and limits on secondary cases.

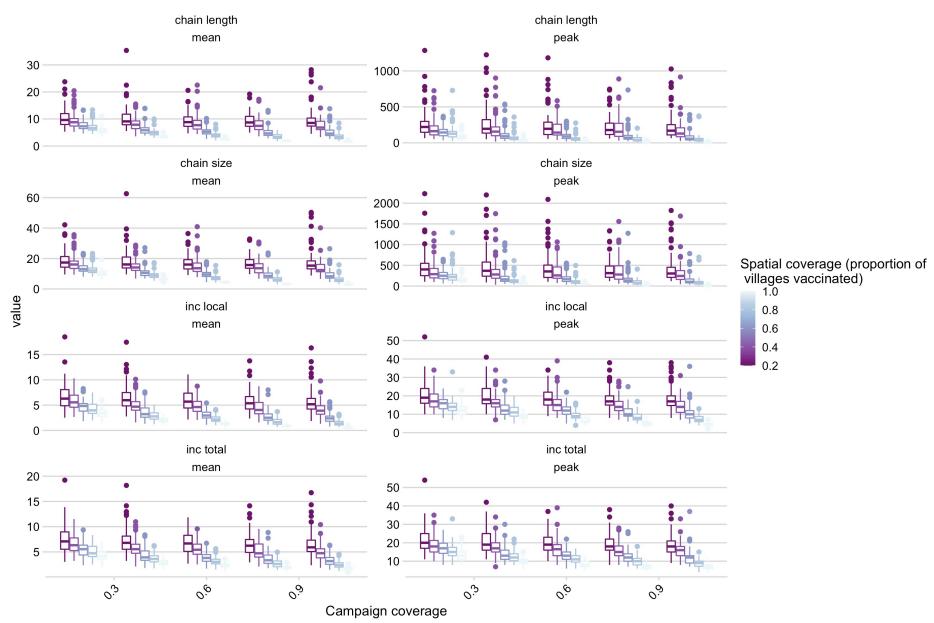


Figure 4.19: Simulation outcomes across a range of campaign coverage and spatial coverage for the baseline case.

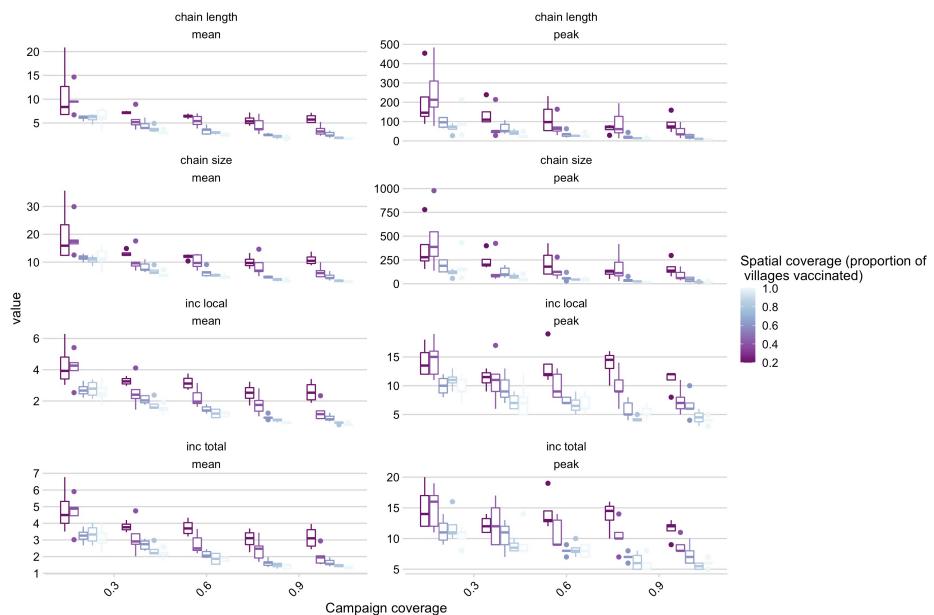


Figure 4.20: Simulation outcomes across a range of campaign coverage and spatial coverage incorporating reductions in the maximum number of secondary cases rate as district coverage increases.

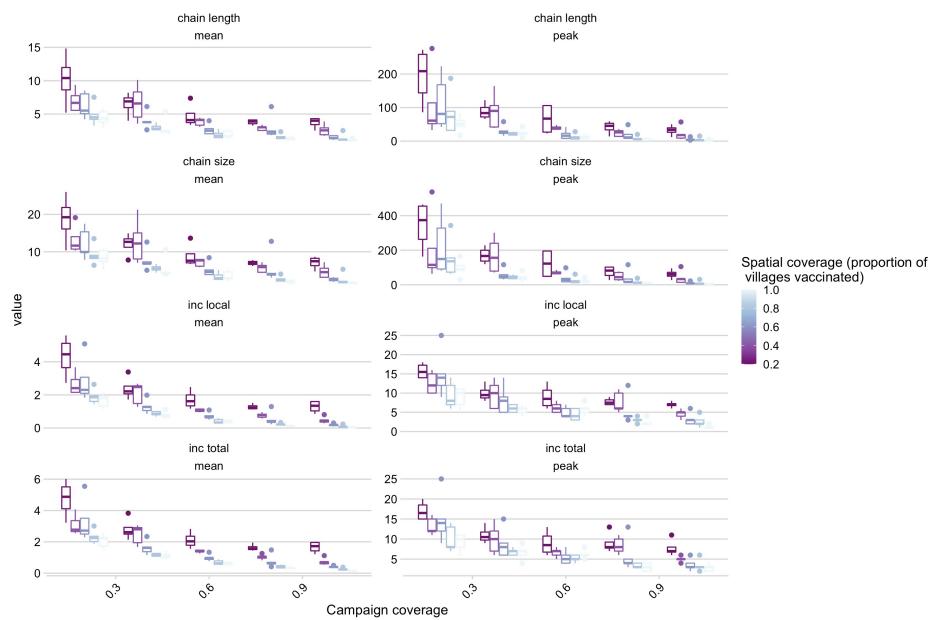


Figure 4.21: Simulation outcomes across a range of campaign coverage and spatial coverage incorporating reductions in the introduction rate as district coverage increases.

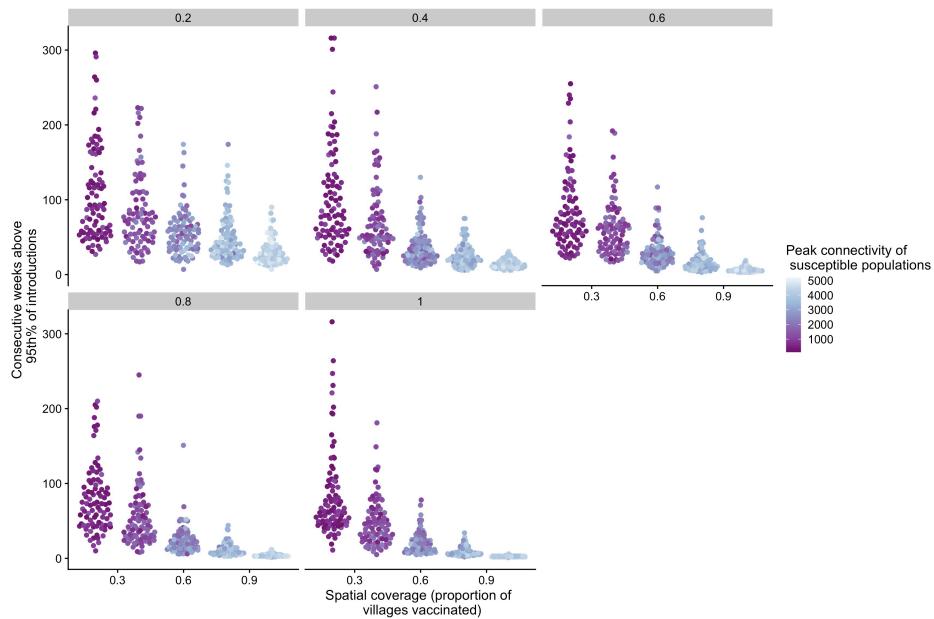


Figure 4.22: Outbreak durations (weeks with cases > 95% of introductions) and their relationship to connectivity of villages across a range of campaign coverage and spatial coverage.

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