

Chapter 20: Modeling canine rabies virus transmission dynamics¹

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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

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1. 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 (Heesterbeek et al., 2015). 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 (Klepac, Metcalf, McLean, & Hampson, 2013). 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.

1.1 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 (Panjeti & Real, 2011). Elimination of fox rabies in Europe was kick-started by modeling studies that demonstrated the feasibility of control (Anderson, Jackson, May, & Smith, 1981). 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 (Murray, Stanley, & Brown, 1986), establishing that landscape features such as rivers act as barriers to disease dispersal (D. L. Smith, Lucey, Waller, Childs, & Real, 2002), and delineating how birth pulses shape seasonality in transmission (Duke-Sylvester, Bolzoni, & Real, 2011). 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 (Cleaveland et al., 2014a). In addition, canine rabies persists in low- and middle-income countries where surveillance capacity is limited and representative disease data are lacking (Scott, Coetzer, Fahrion, & Nel, 2017). Beyond capturing core infection biology, models of canine rabies must also encompass human influences and be tractable to interpretation in data-sparse settings.

1.2 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, Lakshmanan et al., 2006). For canine rabies, evidence suggests that domestic dogs are the reservoir host even in areas with complex wild carnivore communities (Lembo et al., 2008; 2007). 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 (Cleaveland, Lankester, Townsend, Lembo, & Hampson, 2014b).

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 (Hampson et al., 2009). 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 (Foggin, 1988; Hampson et al., 2009; Hemachudha, Laothamatas, & Rupprecht, 2002). 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 (Hampson et al., 2009; Tepsumethanon, Wilde, & Meslin, 2005). 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 (Zhang et al., 2008), 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 (Hampson et al., 2009). 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 (Brunker, Hampson, Horton, & Biek, 2012).

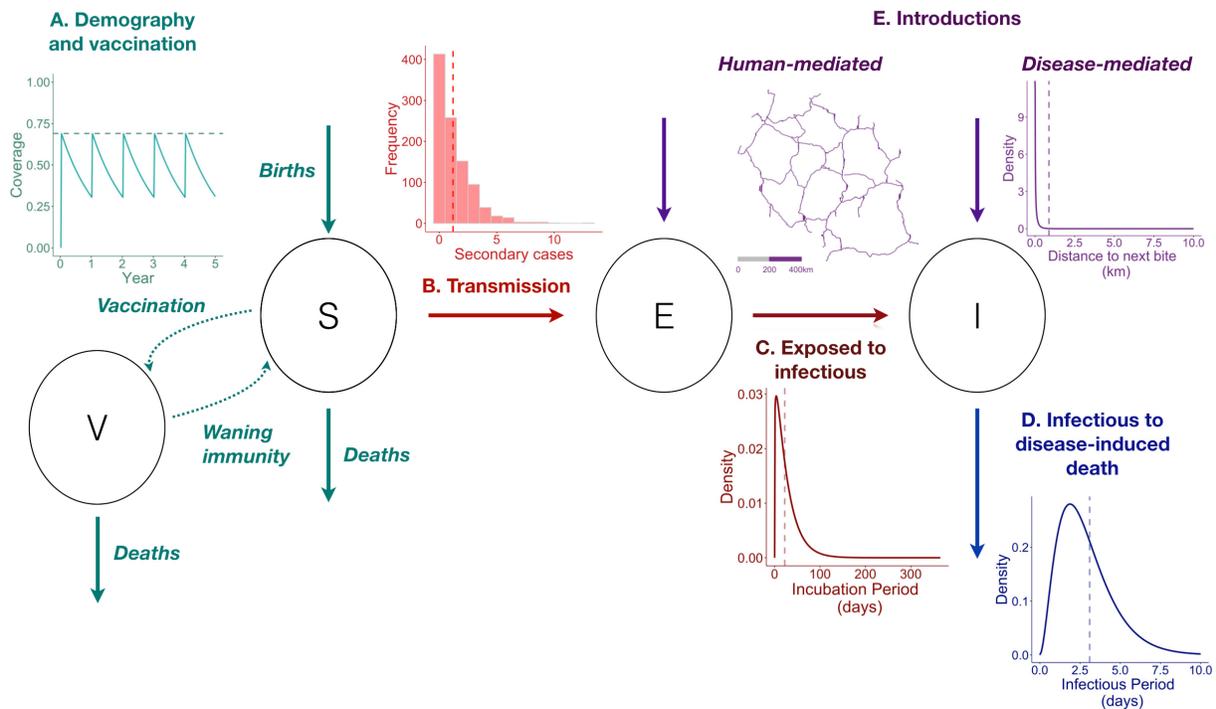


Figure 20.1. The Susceptible-Exposed-Infected-Vaccinated (SEIV) modeling framework for canine rabies: circles indicate epidemiological classes, arrows linking circles indicate how individuals can move between classes, insets describe underlying processes and influences. **A) Host demography (i.e., the 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	Czupryna et al., 2016	A
Death rate	--	Mean annual rate (dogs/yr)	0.42	Czupryna et al., 2016	A
Vaccine waning	--	Mean annual rate (dogs/yr)	0.33	Lakshmanan et al., 2006	A
Secondary cases (R_0)	Negative binomial, mean 1.2 secondary cases	Mean	1.2	Townsend et al., 2013	B
		Dispersion parameter (k)	1.3		
Incubation period	Gamma, mean 22.3 days	Shape	1.15	Hampson et al., 2009	C
		Rate	0.04		
Infectious period	Gamma, mean 3.1 days	Shape	2.9	Hampson et al., 2009	D
		Rate	1.01		
Dispersal kernel	Gamma, mean 0.88 km	Shape	0.215	Townsend et al., 2013	E
		Rate	0.245		

1.3 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 (Lloyd-Smith et al., 2005a). Theory indicates that for diseases with density-dependent transmission, i.e. when transmission scales with host density, there exists a threshold density below which the disease cannot persist (McCallum, Barlow, & Hone, 2001). However, there is no such threshold when transmission is frequency-dependent, i.e. transmission rates are independent of host density (Lloyd-Smith et al., 2005a).

For canine rabies, the basic reproductive number (R_0) or the average number of secondary cases resulting from a single infection in a completely susceptible

population, is generally estimated as between 1-2 (Coleman & Dye, 1996; Hampson et al., 2009; Kurosawa et al., 2017; Townsend, Sumantra, et al., 2013b). Such consistently low estimates of R_0 across a range of dog densities suggest that rabies virus transmission is largely frequency-dependent (Fitzpatrick et al., 2012; Hampson et al., 2009; Tian et al., 2018; Townsend, Sumantra, et al., 2013b; Zinsstag et al., 2009). 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 (Morters et al., 2012).

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 (McCallum et al., 2001). 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 (Keeling & Rohani, 2008). 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 (Hampson et al., 2016). 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 (Ferrari, Perkins, Pomeroy, & Bjørnstad, 2011). Phenomenological approximations may offer a solution to this challenge (Aparicio & Pascual, 2007; Pascual, Roy, & Laneri, 2011), 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 (Ferguson et al., 2015; Townsend, Sumantra, et al., 2013b), 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 (Hampson et al., 2007).

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 (Grassly & Fraser, 2008). 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.

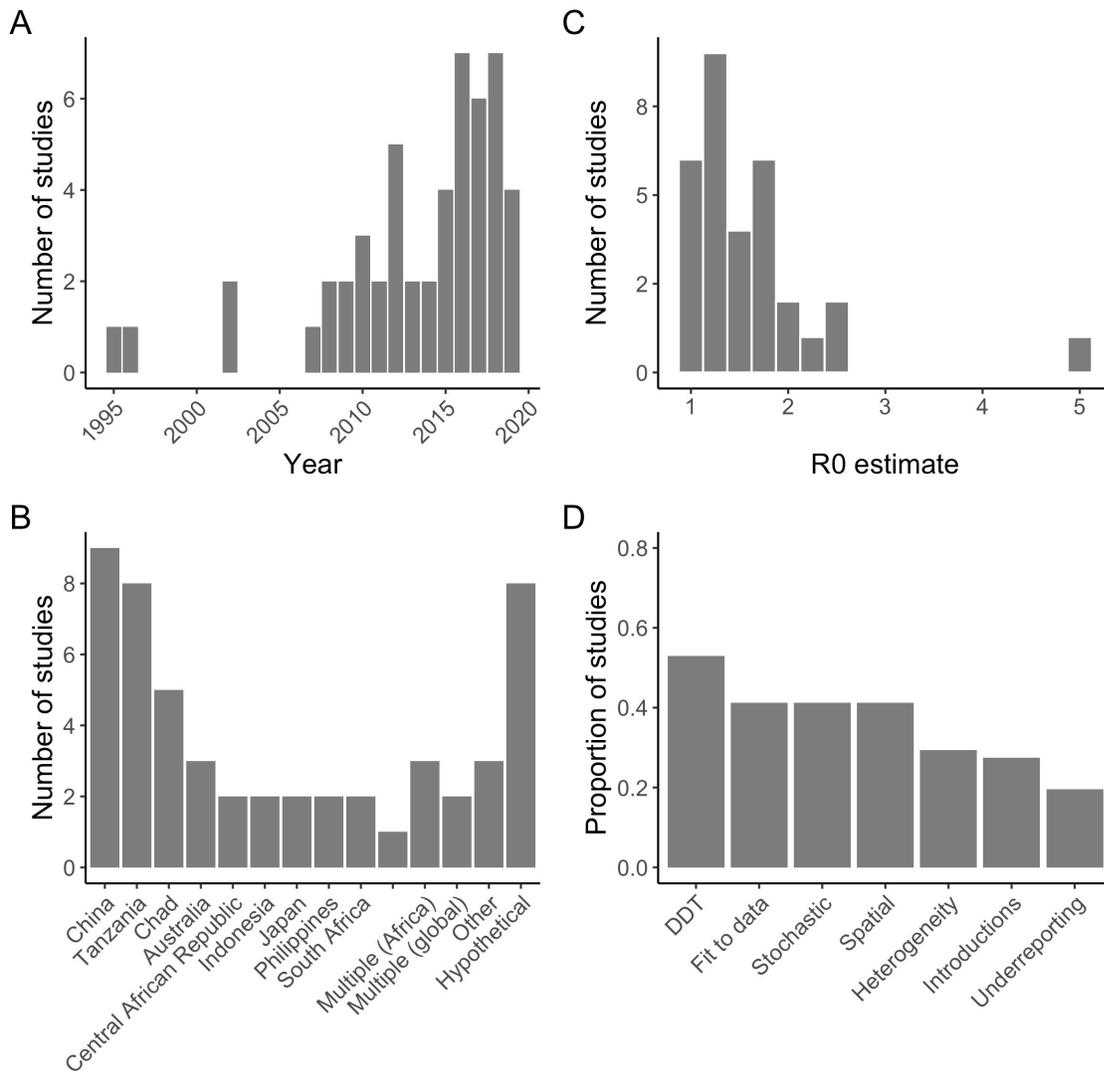


Figure 20.2. Summary of studies with a dynamic model of canine rabies. A total of 51 studies were included. A) Year of publication, with most studies published after 2006; B) Countries where rabies dynamics were modeled: studies were concentrated in China, Tanzania, and Chad, but many also examined dynamics 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.

2. 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 (Rattanavipapong et al., 2018). 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 (Anothaisintawee et al., 2018). 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).

2.1 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 (Ferguson et al., 2015; Townsend, Sumantra, et al., 2013b).

While the critical vaccination threshold (p_c or $1 - 1/R_0$) 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 (Coleman & Dye, 1996; World Health Organization, 2013). 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 (Hampson et al., 2009; Lloyd-Smith, Schreiber, Kopp, & Getz, 2005b).

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 complexities have little impact on the emergent dynamics of infection (Keeling & Rohani, 2008). However, for a disease with lower transmission, heterogeneities may result in unpredictable outbreaks (Grassly & Fraser, 2008). 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 (Townsend, Sumantra, et al., 2013b), 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 (Bourhy et al., 2016; Laager et al., 2019). Human behavior is also a key driver of transmission patterns, facilitating as well as dampening transmission (Brunker et al., 2015). 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 (Brunker et al., 2015; Talbi et al., 2010; Tohma et al., 2016). Road networks have been identified as correlates of phylogenetic distance, indicating that human movement could shape the spatial structure of canine rabies virus (Brunker et al., 2015; Talbi et al., 2010; Tohma et al., 2016). There is also strong phylogenetic evidence that historical human-mediated long-distance movements underlie much of the contemporary global distribution of canine rabies (King, Fooks, Aubert, & Wandeler, 2004). 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 (Bjørnstad & Grenfell, 2008), 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 (Hudson, Brookes, Ward, & Dürr, 2019; Laager et al., 2018; Wilson-Aggarwal et al., 2019). 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 (Fitzpatrick et al., 2014; Hampson, Cleaveland, & Briggs, 2011; Zinsstag et al., 2009). 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 (Hampson et al., 2015; Knobel et al., 2005; WHO Rabies Modelling Consortium, 2019). These more recent studies demonstrate that PEP is still a very cost-effective intervention even when accounting 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 (Tarantola et al., 2018). 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 (WHO Rabies Modelling Consortium, 2019), but more investment and commitment is still needed.

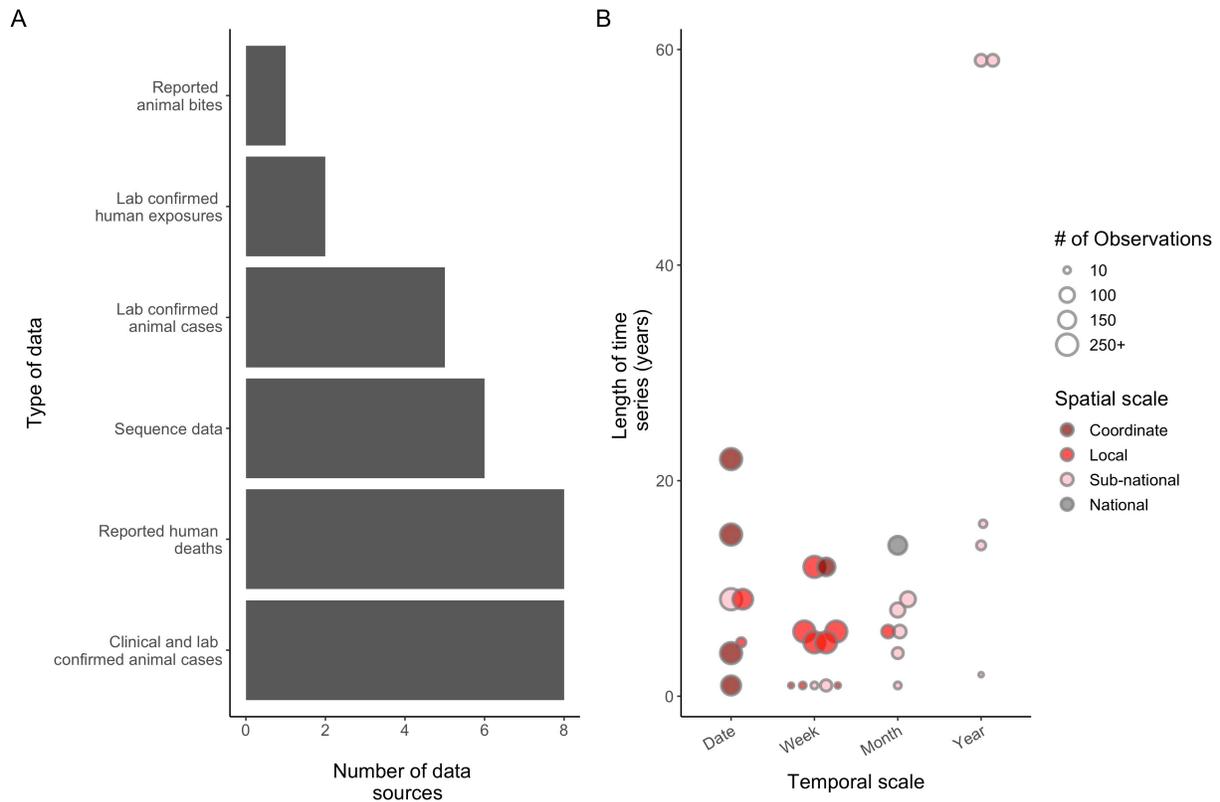


Figure 20.3. Rabies data reported in modeling studies ($N = 25$ studies reporting 30 unique data sources). A) Type of data used. B) The scales of temporal (x-axis) and spatial (colors) information available and the duration (y axis). The size of the points is proportional to the number of observations 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. 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, (Beyer et al., 2010; Cori et al., 2018; Mollentze et al., 2014) 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 (Townsend, Lembo, et al., 2013a).

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.

3.1 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 (Changalucha et al., 2018; Hampson et al., 2008). In settings where PEP is provided for free and indiscriminately, a higher proportion of reported bites may be due to non-rabid animals (Rajeev et al., 2018; Rysava et al., 2018; Wallace et al., 2015), and many Category 1 exposures, i.e. those for which PEP is not indicated (“Rabies

vaccines: WHO position paper,” 2018), receive unnecessary PEP (Duong et al., 2016; Rajeev et al., 2018; Tenzin, Dhand, & Ward, 2011).

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.

3.2 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 (Scott et al., 2017; Townsend, Lembo, et al., 2013a). 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 (Dacheux et al., 2008). 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 (Wentworth et al., 2019). 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 (Léchenne et al., 2016). 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 (Undurraga et al., 2017). 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.

3.3 Sequence data

Sequence data can be used to make inferences about transmission processes, particularly when linked with epidemiological data (Bourhy et al., 2016; Brunker et al., 2015; 2018; Cori et al., 2018; Talbi et al., 2010; Zinsstag et al., 2017). Recent studies have demonstrated the added value of whole-genome sequencing (WGS) for understanding finer scale transmission dynamics of canine rabies (Brunker et al., 2015; 2018), 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 (Léchenne et al., 2016). Bioinformatic pipelines and open sharing of sequences, such as those developed for other viral pathogens (Hadfield et al., 2018), 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.

3.4 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 (Brunker et al., 2018). 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 (Zinsstag et al., 2017). 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 (Gibson et al., 2015; Sambo et al., 2017; Tenzin et al., 2015). 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.

4. 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.

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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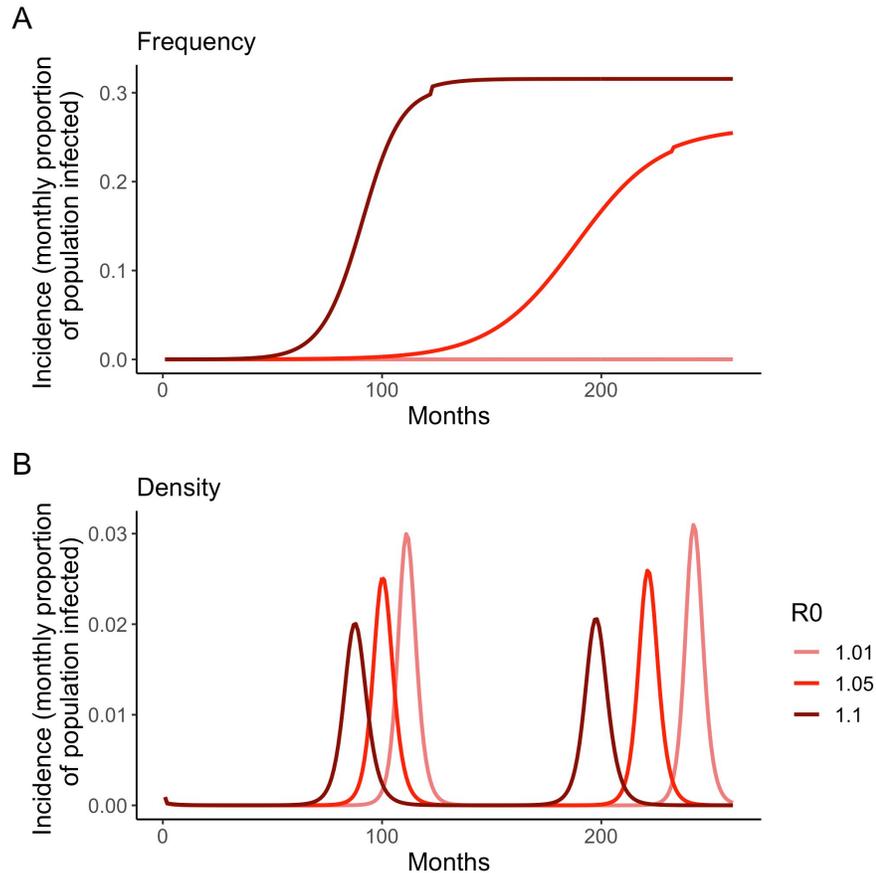
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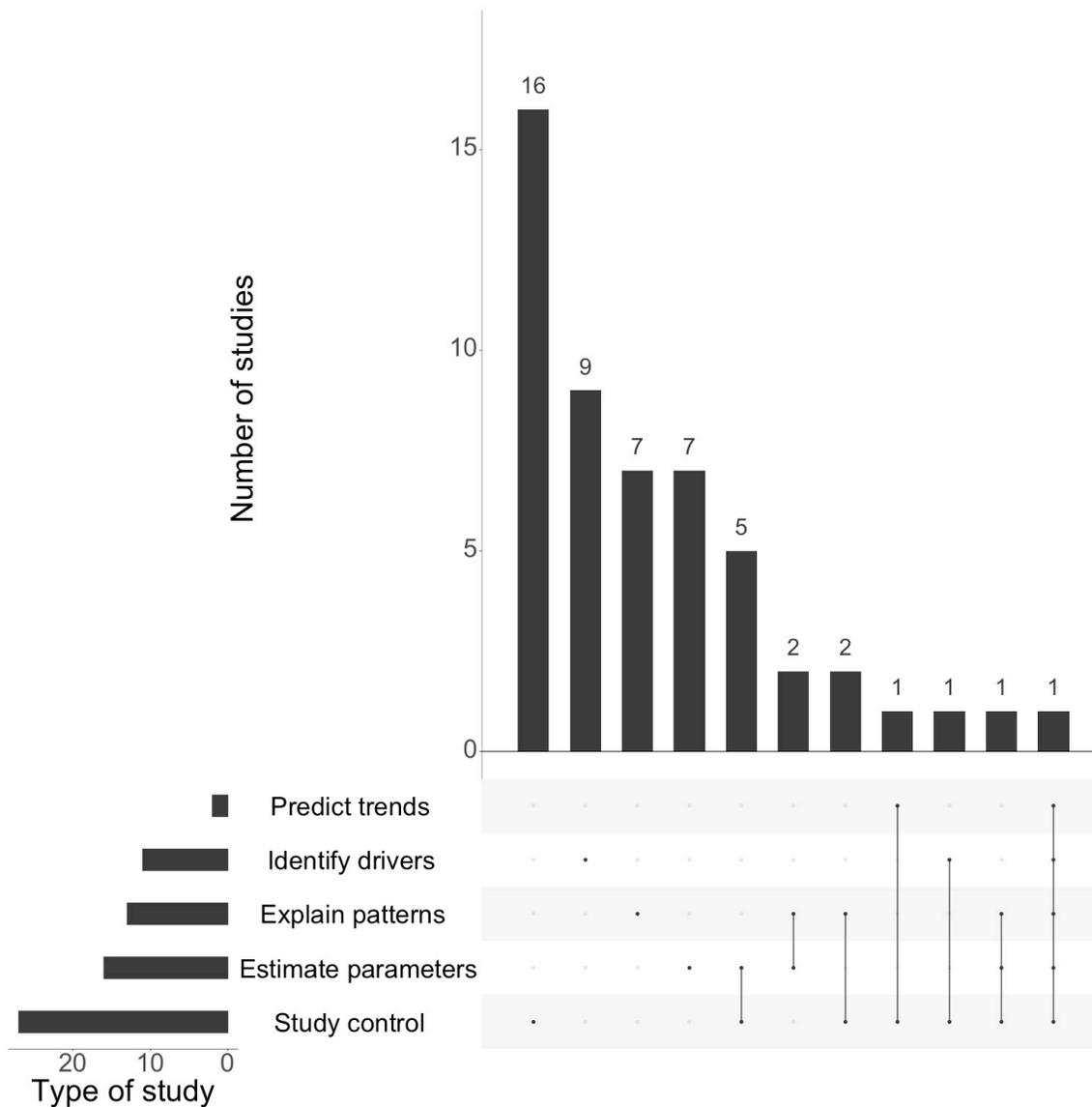
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Supplementary Figures



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).