Reassessing global historical $\mathcal{R}_0$ estimates of canine rabies

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Abstract

Rabies spread by domestic dogs continues to cause tens of thousands of human deaths every year in low- and middle-income countries. Despite this heavy mortality burden, rabies is often neglected, perhaps because it has been effectively controlled from high-income countries through mass dog vaccination. Estimates of the intrinsic reproductive number ($\mathcal{R}_0$) (a metric disease spread risk) of canine rabies from a wide range of times and locations are low (values <2), with narrow confidence intervals compared to many infectious diseases. This consistent narrow range of estimates across historical outbreaks is surprising. We combined incidence data from historical outbreaks of canine rabies from around the world (1917-2003) with high-quality contact-tracing data from Tanzania (2002-present) to investigate initial growth rates (r_0), generation-interval distributions (G) and reproductive numbers ($\mathcal{R}_0$). We updated earlier work by: choosing outbreak windows algorithmically; fitting r_0 using a more appropriate statistical method that accounts for decreases through time; and propagating uncertainty from both r_0 and G when estimating $\mathcal{R}_0$. Our $\mathcal{R}_0$ estimates are larger than previous estimates, with wider confidence intervals. Our novel hybrid approach for estimating $\mathcal{R}_0$ and its uncertainty is applicable to other disease systems where researchers estimate $\mathcal{R}_0$ by combining estimates of r_0 and G.

Introduction

Canine rabies, primarily spread by domestic dogs, is a vaccine-preventable disease that continues to cause tens of thousands of human deaths every year in low- and middle-income countries (LMICs) (Taylor et al., 2017; Minghui et al., 2018). Canine rabies has been effectively eliminated from high-income countries by mass dog vaccination (Rupprecht et al., 2008). Despite the effectiveness of vaccinating dogs, rabies continues to cause many human deaths and large economic losses in LMICs due to the limited implementation of rabies control strategies (Hampson et al., 2015). The past two decades have seen an increase in rabies control efforts — including dog vaccination campaigns and improvements in surveillance (Kwoba et al., 2019; Mtema et al., 2016; Gibson et al., 2018; Mazeri et al., 2018; Wallace et al., 2015). The World Health Organization (WHO) and partners (OIE, FAO, GARC) joined forces to support LMICs in eliminating human deaths from dog-mediated rabies by 2030 (Minghui et al., 2018; Abela-Ridder et al., 2016). Mass dog vaccination campaigns have begun in some LMICs and are being scaled up (Castillo-Neyra et al., 2019; Evans et al., 2019). However, the emergence of SARS-CoV-2 pandemic have greatly disrupted and paused the efforts of rabies control and elimination strategy (Nadal et al., 2022). As SARS-CoV-2 pandemic is transitioning out of global emergency, rabies control programmes are slowly unpaused. An understanding of rabies epidemiology — in particular, reliable estimates of the basic reproductive number ($\mathcal{R}_0$), a quantitative measure of disease spread that is often used to guide vaccination strategies — could inform rabies control efforts.

$\mathcal{R}_0$ is defined as the expected number of secondary cases generated from each primary case in a fully susceptible population (Macdonald, 1952). Estimates of $\mathcal{R}_0$ using various methods (i.e., direct estimates from infection histories, epidemic tree reconstruction, and epidemic curve methods) based on historical outbreaks of rabies have generally been surprisingly low, typically between 1 and 2 with narrow confidence intervals for variety of regions and time periods (Hampson et al., 2009; Kurosawa et al., 2017; Kitala et al., 2002). With such a low $\mathcal{R}_0$ one might expect rabies to fade out from behavioural control measures combined with stochastic fluctuations, even in the absence of vaccination. In contrast to diseases with $\mathcal{R}_0$ (e.g., rinderpest with $\mathcal{R}_0 \approx 4$ (Mariner et al., 2005)), $\mathcal{R}_0$ estimates for rabies imply that control through vaccination should be relatively easy. With such a low $\mathcal{R}_0$ one might expect rabies to fade out from behavioural control measures combined with stochastic fluctuations, even in the absence of vaccination.

Here we revisit and explore why rabies, with low $\mathcal{R}_0$, nonetheless persists in many countries around the world. Such persistence suggests that rabies's potential for spread, and therefore the difficulty of rabies control, may have been underestimated. In this paper, we will combine information derived from epidemic curves with a high-resolution contact tracing dataset that provides large number of observed generation intervals (which is rare for infectious disease studies) to estimate $\mathcal{R}_0$.

Materials and Methods

$\mathcal{R}_0$ is often estimated by combining two other epidemiological quantities: the initial growth rate of an epidemic (r_0) and the generation interval (G) distribution, where a G is defined as the time between successive infections along a transmission chain (Park et al., 2018). The growth rate r_0 is often estimated by fitting a growth rate to time series data from the early stages of epidemics. G is an individual-level quantity that measures the time between an individual getting infected to infecting another individual. The generation interval distribution is the natural way to link r_0 and $\mathcal{R}_0$ (Wallinga and Lipsitch, 2006; Champredon and Dushoff, 2015). During an outbreak in a fully susceptible population, $\mathcal{R}_0$ can be calculated from r_0 and the G distribution by the Euler-Lotka equation (Wallinga and Lipsitch, 2006)

$$\mathcal{R}_0 = \frac{1}{\sum_{t=1}^{\infty} G(t)e^{-rt}}, \tag{1}$$

where t is time, and $G(t)$ is the generation interval distribution. This formula is convenient to calculate point estimates of $\mathcal{R}_0$; however, propagating uncertainty from the estimates of r_0 and the G distribution spontaneously has not been done often in practice.

Initial growth rate

Disease incidence typically increases approximately exponentially during the early stages of an epidemic. The initial growth rate r_0 is often estimated by fitting exponential curves from near the beginning to near the peak of an epidemic. However, growth rates estimated from an exponential model can be biased downward, overconfident, and sensitive to the choice of fitting windows (Ma et al., 2014). Here we used the logistic curves provide more robust estimates of r_0 (Ma et al., 2014; Chowell, 2017).

We select fitting windows algorithmically for each outbreak as follows: 1) we broke each time series into "phases", a new phase starts after a peak of height at least `minPeak` cases followed by a proportional decline of at least `declineRatio`; 2) In each phase, we identify a prospective fitting window starting after the last observation of 0 cases and extending one observation past the highest value in the phase (unless the highest value is itself the last observation); 3) we then fit our model to the cases in the fitting window if (and only if) it has a peak of at least `minPeak` cases, a length of at least `minLength` observations, and a ratio of at least `minClimb` between the highest and lowest observations. We tried a handful of parameter combinations before settling on a final set during an expert consultation. These explorations are detailed, and the final choices noted, in our code repository.

Observed Generation intervals

Transmission events are generally hard to observe for most diseases. In an earlier, influential rabies paper, estimated generation intervals were constructed by summing two quantities: a latent period (the time from infection to infectiousness), and a wait time (time from infectiousness to transmission) (Hampson et al., 2009). Since clinical signs and infectiousness appear at nearly the same time in rabies, the incubation period (the time from infection to clinical signs) is routinely used as a proxy for the latent period. In the Hampson et al. analysis, latent (really, incubation) periods and infectious periods were randomly and independently resampled from empirically observed distributions (Hampson et al., 2009), and then waiting times sampled uniformly from the selected infection periods.

However, this approach for constructing G values (i.e., summing independently resampled values of incubation and infectious periods) does not account for the possibility of multiple transmissions from the same individual, nor does it account for correlations between time distributions and biting behaviour. Figure 1 illustrates the generation intervals of a single transmission event from a rabid animal (comprising a single incubation period plus a waiting time) and multiple transmission events from a rabid animal (comprising a single incubation period and three waiting times). For diseases like rabies, where transmissions links (and generation intervals) are observable, multiple transmissions and possible correlation structures are all implicitly accounted for within the observation processes through contact tracing.

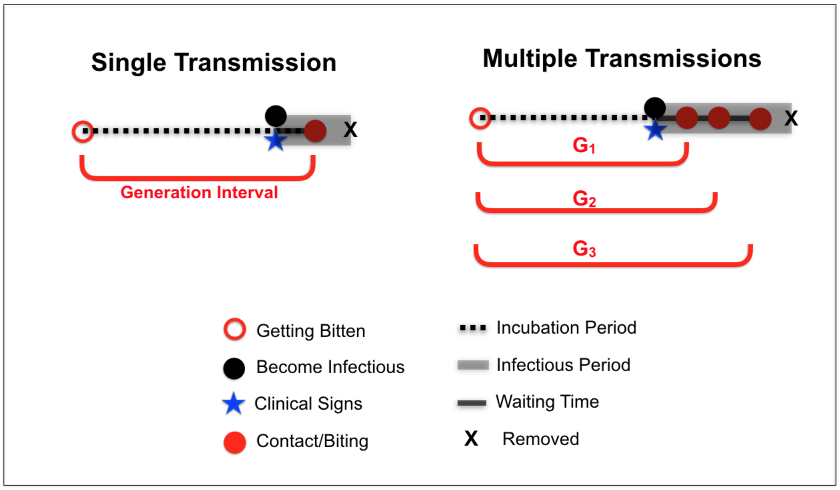

Figure 1: **Decomposing generation intervals.** Generation intervals start when a focal animal acquires infection (open red circle) and end after a period of viral replication (dashed line) when an animal shows clinical signs (blue star), becomes infectious (solid black circle) and infects another animal — in rabies the onset of clinical signs and of becoming infectious are closely synchronized. Once the infectious period (grey block) starts, there is a wait time (solid black line) until a susceptible host (solid red circles) is bitten. The infectious period ends with the death of the focal host (black X). The generation interval is the interval between getting infected and infecting a new case (red interval between open and solid circles). (right) If a single biter transmits multiple times, the wait times are generally different, but the incubation period is the same for each transmission event.

Correcting for vaccination

In a population where some animals are not susceptible, calculations based on estimates of r_0 and the G distribution (1) estimate the *realized* average number of cases per case, also known as the effective reproductive number $\mathcal{R}_e$. In the case of rabies, vaccination is the only known cause of immunity (case fatality in dogs is believed to be 100%). For a given population with ν vaccination proportion, the estimated $\mathcal{R}_0$

with vaccination correction is the following:

$$\mathcal{R}_0 = \frac{\mathcal{R}_e}{(1-\nu)}. \tag{2}$$

Data and material

We used data from December 2002 – November 2022, from an ongoing contact tracing project in Tanzania (Hampson et al., 2008, 2009). Since 2002, there are 8636 domestic dog recorded events (i.e., domestic dogs bitten by an animal), and 3552 suspected rabid dogs in the Serengeti, Tanzania. Transmission events were documented through retrospective interviews with witnesses, applying diagnostic epidemiological and clinical criteria from the six-step method (Tepsumethanon et al., 2005). Each dog was given a unique identifier and date of the bite and clinical signs were recorded if applicable and available. 2132 of dog transmissions were from unidentified domestic animals or wildlife. We restricted our analysis in this paper to domestic dog transmissions (i.e., dog to dog), and obtained 293 directly observed generation intervals (i.e. both biter and secondary case have time bitten recorded). There were four observed dogs with multiple exposures (i.e., bitten by different identified biters), generating extra generation intervals, but it is unclear which transmission event transmitted rabies to these dogs. For simplicity, we omitted these four dogs and their generation intervals from our analysis.

Fitting and Propagating Parameter Uncertainties

To propagate uncertainties for both r_0 and G, we used a hybrid approach. We first fitted logistic models, with negative binomial observation error, to incidence data to estimate r_0 implemented in the R package "epigrowthfit" Jagan et al. (2024). We then compute a sample of 1000 $\hat{\mathcal{R}}_0$ values using equation (2); for each value of $\hat{\mathcal{R}}_0$, we first draw a value of $\hat{r_0}$ from a normal distribution from the estimates of the logistic fit and an independent sample of G from the empirical contact tracing data. To sample G from the empirical contact tracing data, we first take a weighted sample 100 biters which accounts for biter level variation, and for each biter, we sample a G from its respective transmission event to account for individual variation. We then matched samples of G to the r_0 samples to produce a range of estimates for $\mathcal{R}_0$. This hybrid sampling approach incorporates both sources of uncertainties from r_0 and G. when calculating $\mathcal{R}_0$ estimates. Finally, we take the 2.5, 50, 97.5% percentiles of the distribution of $\mathcal{R}_0$ estimates for each rabies outbreak.

Results

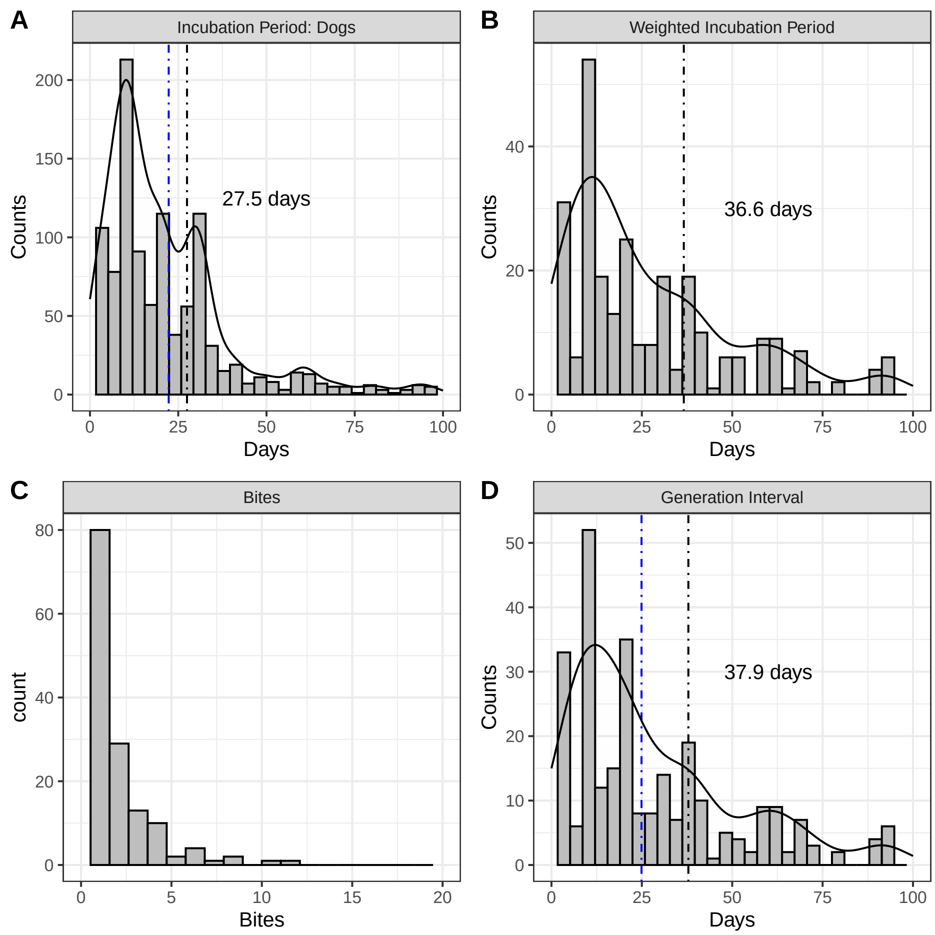

Figure 2: **Time intervals and biting empirical distributions from contact tracing data.** Panel A is the distribution of observed incubation periods. Panel B is the distribution of incubation periods weighted by each dog's biting frequency (Panel C). The weighted distribution corresponds to the contribution of incubation periods to generation intervals (Panel D). Black dash lines show the means of each time-interval distribution and dash blue lines shows the means incubation period and generation interval (22.3 and 24.9 days) reported in (Hampson et al., 2009).

Figure 2 shows the empirical distributions of the observed incubation periods, rabid dog biting frequency, and generation intervals from contact tracing data. The mean observed incubation period is 27.5 days (n = 1109 dogs), the mean biting frequency is 1.65 bites per rabid dog, and the weighted mean incubation period is 36.6 days (n = 143 biting dogs). The mean observed generation interval is 37.9 days (n = 143 primary infections resulting in 293 secondary cases), which is significantly larger than the mean generation interval constructed from independently summing incubation periods and wait times (24.9 days (Hampson et al., 2009)). The weighted incubation period distribution more closely resembles the generation interval distribution than the incubation period of all dogs.

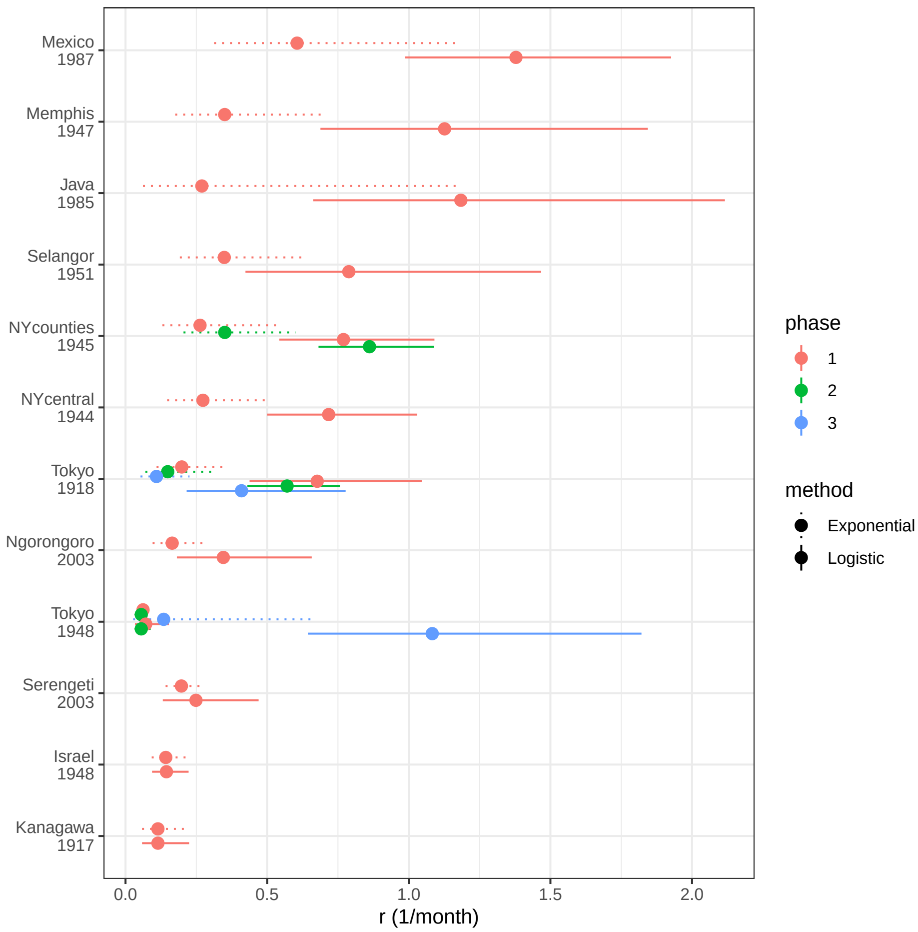

Figure 3: **Growth rate estimates for global historical outbreaks of rabies.** Estimates and 95% confidence intervals of r_0 in global historical outbreaks estimated from exponential (dotted) and logistic (solid) model fits.
Different colors represents different phases from the times series data.

We estimated r_0 from historical outbreak data (Figure 3). For a direct comparison of the method used in (Hampson et al., 2009), we also estimated r_0 from an exponential model. Both methods (exponential and logistic) were applied to all phases of the global historical outbreaks. Overall, r_0 estimates from the logistical model are larger with wider confidence intervals compared to r_0 estimates from the exponential model (i.e. the estimation method used in (Hampson et al., 2009)).

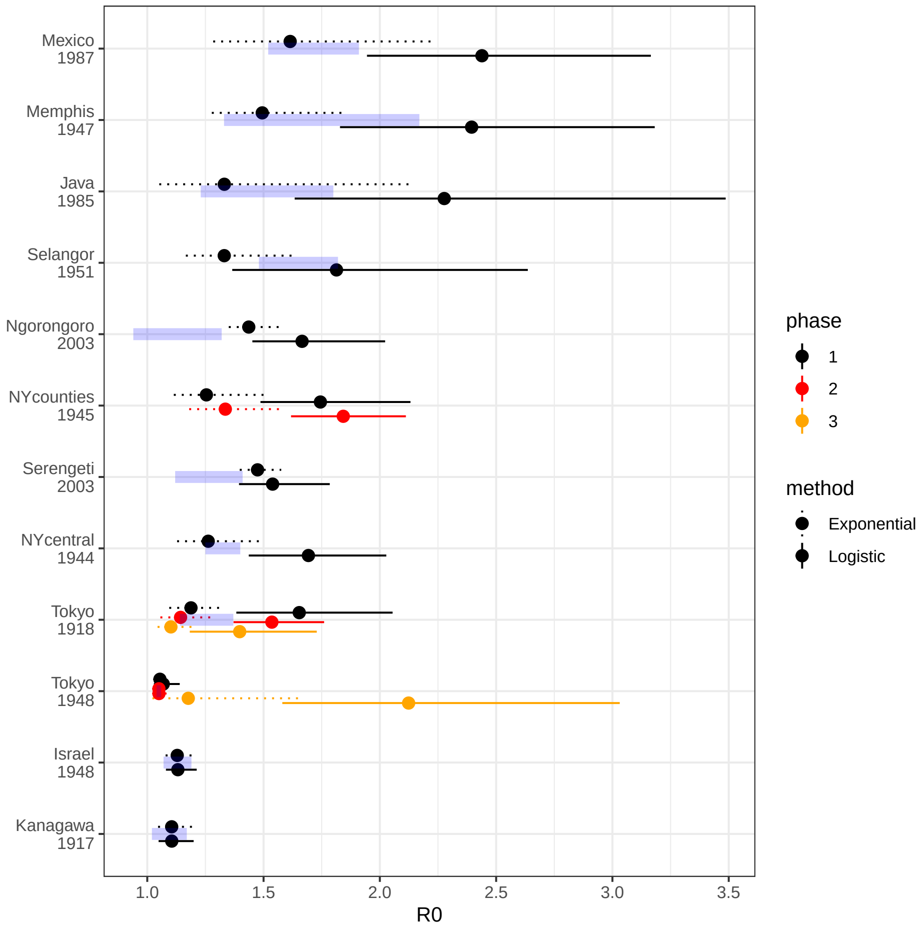

Figure 4: **Reproductive number estimates for global historical outbreaks of rabies**
Previous estimates of $\mathcal{R}_0$ are shown in blue highlights; $\mathcal{R}_0$ estimates and confidence interval (95% quantiles from the estimated $\mathcal{R}_0$ sample) from our hybrid approach using exponential (dotted lines) and logistic (solid lines). $\mathcal{R}_0$ are corrected for vaccination coverage.ML: todo: add dates to location name.

We combined our estimates of r_0 from the logistic model with the empirical G from our detailed Tanzanian data to produce $\mathcal{R}_0$ estimates. Of the listed historical outbreaks, four occurred in locations with prior rabies vaccination coverage: Memphis, US (1947, 10% vaccine coverage); Serengeti, Tanzania (2003, 20% coverage);

Ngorongoro, Tanzania (2003, 20% coverage); and Sultan Hamad, Kenya (1992, 24% coverage). Figure 4 shows the $\mathcal{R}_0$ estimates using various approaches along with estimates from Hampson et al. (2009). Our estimates of $\mathcal{R}_0$ using the logistic model and corrected G are larger than previous reported (Hampson et al., 2009) with 3 locations (Java, Memphis and Mexico) having $\mathcal{R}_0$ greater than 2. The hybrid approach provides larger values of $\mathcal{R}_0$ and wider confidence intervals after propagating uncertainty from both r_0 and generation interval distributions with upper confidence intervals greater than 2 for most locations.

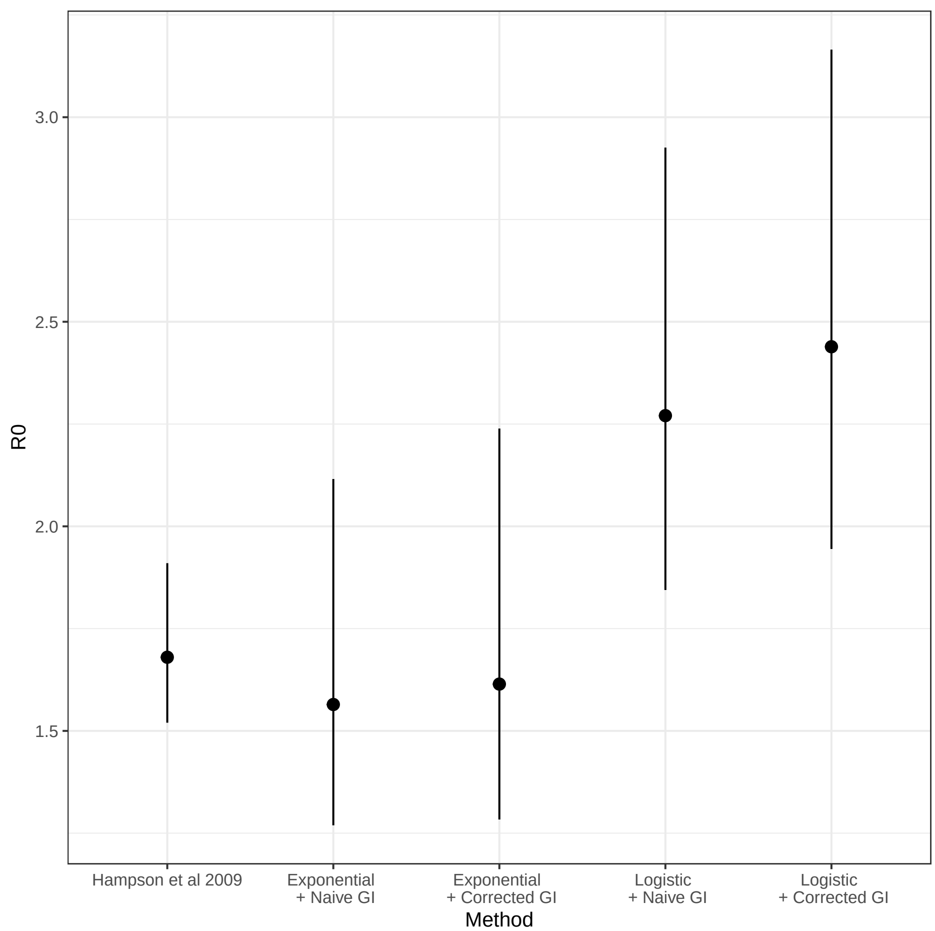

Figure 5: **Effects of r_0, corrected G on the estimates of $\mathcal{R}_0$ in Mexico outbreak.** Exponential r_0 and naive G is the analgous fitting to Hampson et al. (2009) using our algorithmic windowing selection. $\mathcal{R}_0$ using logistic to estimate r_0 is larger than exponential and corrected G increase $\mathcal{R}_0$ and uncertainty.

Lastly, we compare the effects of different estimation techniques of r_0 and G on estimates of $\mathcal{R}_0$ (Figure 5). For illustrative purposes, we used the 1987 outbreak in Mexico where there was no vaccination. Propagating uncertainty from both r_0 and G generally leads to wider confidence intervals compared to previous $\mathcal{R}_0$ estimates in Hampson et al. (2009). $\mathcal{R}_0$ estimate increases when we estimate r_0 via the logistic model, or G instead of the naive constructed approach in Hampson et al. (2009) . The overall effect of $\mathcal{R}_0$ increases even more when included both corrections (i.e., in r_0 and G) with even larger uncertainty.

Discussion

Our study has enlighten the mystery of rabies persistence despite the fact that $\mathcal{R}_0$ estimates in historical outbreaks have been consistently low, by showing that substantially higher basic reproduction numbers are compatible with historical outbreak data than previous thought. Here, we reanalyzed historical rabies epidemics with improved model assumptions and uncertainty propagation, showing that historical estimates of $\mathcal{R}_0$ were downward biased and overconfident.

The basic reproductive number $\mathcal{R}_0$ is commonly used to summarize the risk of infectious disease and to inform control measures. Here, we used a relatively simple approach to estimate $\mathcal{R}_0$ by combining initial growth rate (r_0) estimates from incidence data and generation intervals from contact tracing data. By assuming rabies generation intervals are similar biologically, this method allows us to use detailed contact tracing data from Tanzania with incidence data to estimate We improved on earlier work by correcting for slowdown in growth when estimating r_0, and by developing an approach to propagate uncertainty from both r_0 and G, resulting in higher $\mathcal{R}_0$ estimates with wider confidence intervals.

Estimates of $\mathcal{R}_0$ are strongly affected by estimates of the growth rate during the initial phase of the epidemic. The logistic model gives a better approximation of the initial phase of the epidemic resulting in a larger estimate of r_0 compared to the exponential model (Ma et al., 2014). Our estimates of r_0 account for observation error (measurements may not perfectly match reality), but not for process error (the fundamental stochasticity of the system itself). Thus, there may be more uncertainty in r_0 than we estimate (King et al., 2015).

Re-analysis of these data also allowed us to identify an overlooked fact about rabies generation intervals: observed generation intervals are longer on average than intervals constructed by naively adding incubation period and waiting time, because of within-individual correlations in time distributions and biting behaviour. The unexpected importance of these correlations could have implications for G-based studies of other infectious diseases as it can bias the estimation of generation intervals as shown in this study. Further investigation of how these correlations affect the overall dynamics of rabies is warranted.

Nevertheless, our estimates suggest that rabies $\mathcal{R}_0$ may be larger, and more uncertain, than previously thought. This finding may explain some of the formerly unexplained variations in the success of rabies-control programs (e.g., low levels of coverage (30–50%) have been successful in some settings while high coverage 75% was not enough to control rabies in others (Eng et al., 1993)). While our primary goal was to understand why estimates of rabies $\mathcal{R}_0$ were small with narrow confidence intervals, our analysis also revealed an interesting biological process through the lense of generation interval from contact tracing data, the need to account for biting behaviour in the incubation period distribution to match the generation interval distribution. $\mathcal{R}_0$ is typically used as a first approximation for interventions such as vaccination to determine herd immunity thresholds. However, the main heterogeneity in contacts and correlations with incubation periods observed through the generation interval may suggest that simple $\mathcal{R}_0$ estimation methods may be inadequate and should be used with caution. Rabies is a nice system to hightlight this effect because of the nature of the disease that transmission events and clinical signs are observable with contact tracing. The correlation effect can be have important implications to study other disease systems in general, however generation intervals are not always observable like rabies and the uncertainties may be even greater.

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