Title: Rabies shows how scale of transmission can enable acute infections to persist at low prevalence

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Abstract

How acute pathogens persist and what curtails their epidemic growth in the absence of acquired immunity remains unknown. Canine rabies is a fatal zoonosis that circulates endemically at low prevalence among domestic dogs in low- and middle-income countries. We traced rabies transmission in a population of 50,000 dogs in Tanzania from 2002-2016

and applied individual-based models to these spatially resolved data to investigate the mechanisms modulating transmission and the scale over which they operate. While rabies prevalence never exceeded 0.15%, we found significant depletion of susceptible animals that occurred at local scales because of clusters of deaths and dogs already incubating infection. Individual variation in rabid dog behaviour facilitated virus dispersal and co-circulation of virus lineages, enabling metapopulation persistence. These mechanisms have important implications for prediction and control of pathogens circulating in spatially structured populations.

One-Sentence Summary: Identifying the spatial scale of contacts reveals the mechanisms that limit the size of rabies outbreaks and facilitate persistence.

Main Text: Understanding the processes that regulate endemic disease dynamics remains a long-standing challenge in epidemiology (1, 2) and the mechanisms that enable long-term persistence at low prevalence remain largely unexplored (3). This is particularly true for canine rabies, a fatal zoonotic virus for which naturally acquired immunity has not been demonstrated. The basic reproductive number R_0 of rabies that is defined by the expected number of secondary cases produced by a typical infectious individual in a fully susceptible population (4) is low (between 1.1 and 2) and is relatively insensitive to dog density (5), making the disease amenable to elimination through dog vaccination (6). Yet, dog-mediated rabies remains endemic across Africa and Asia where it kills tens of thousands of people every year (7) and its persistent circulation at such low prevalence in largely unvaccinated populations is an enduring enigma.

Rabies is, however, a uniquely tractable system for understanding how population-level patterns of infection emerge from pathogen transmission at the individual level. Rabies is transmitted via bites, which can often be observed, and the clinical signs are readily identifiable, with infected animals typically dying within one week of disease onset (Fig. 1E). Capitalising on these distinctive characteristics, we conducted exhaustive contact tracing to generate spatially resolved data on rabies infection and transmission in Serengeti district, Northern Tanzania, between January 2002 and December 2015. Serengeti district adjoins other populated districts to the north and west, and Serengeti National Park to the southeast (Fig. 1A). We previously showed that domestic dogs maintain rabies in this part of Tanzania, with infrequent spillover to wildlife and spillback to domestic dogs (8). In Serengeti district's population of around 50,000 dogs (and 250,000 people) we traced 3612 rabies infections (Fig. 1, comprising 3081 cases in dogs, 75 in cats, 145 in wildlife and 311 in livestock), along with 6684 potential transmission events to other animals and 1462 people bitten by rabid animals of whom 44 died from rabies. Most identified

cases could be statistically linked to plausible progenitors, indicating that contact tracing detected most cases. Further analysis indicated 83-95% of cases were detected, with missed cases mainly being those generating limited, if any, onward transmission (9). These data show that, despite local vaccination effort (coverage varying between 10 and 40%, fig. S3B), rabies circulated continuously with a maximum prevalence of just 0.15%.

Endemic diseases are thought to be primarily regulated by the depletion of susceptible hosts, typically through disease-induced (or vaccine-acquired) immunity, counterbalanced by births of susceptibles and deaths (4). Yet the very low prevalence and absence of acquired immunity for rabies indicates that large-scale depletion of susceptible hosts is negligible, challenging this explanation as a mechanism for persistence. We estimated dog densities at high spatial resolution through a district-wide census, georeferencing almost 36,000 households and recording the vaccination status of dogs [in this setting almost all dogs are owned but also free-roaming and there are no feral dogs (10)]. Although we saw no clear relationship between dog population density and contact rate when examining dogs bitten per rabid dog (Fig. 1C), mapping rabies infections revealed a small, yet significantly higher incidence of cases in higher density areas (Fig. 1C), suggestive of density-dependent processes. These observations are difficult to reconcile: how does transmission respond to dog population density and what processes keep prevalence so low?

Here, we propose that understanding the fine-scale structure of rabies transmission networks is critical to explaining its persistent dynamics and can inform its control and eventual elimination. We used the serial interval distribution - defined as the interval between the onset of infection in

primary and secondary cases - and movement of traced rabid dogs to reconstruct transmission trees, comprising putative introductions into the district and descendent chains of transmission. Over the 14 years we estimated around 238 introductions (8-24 per year) that led to onward circulation, most likely spreading from neighbouring villages (movie S1). Twenty-two transmission chains, accounting for >70% of cases, circulated for over 12 months (including two for over 4 years), illustrating how co-circulation of lineages contributes to persistence within a metapopulation (Fig. 2). We applied an individual-based model, seeded by these introductions, to the spatially resolved case and dog density data to investigate the processes modulating transmission, the scale over which they operate, and how they facilitate these metapopulation dynamics.

We examined the effect of host (dog) density on contact (biting) within our stochastic individual-based model, drawing from predator-prey functional response theory (11), to fit parameters defining the transmission process in relation to host density (12). We fitted the parameters assuming susceptible and infected dogs were well mixed at different scales ranging from the whole district to within 0.25 km^2 grid cells (fig. S2). The best-fitting parameters at each scale differed in their simulation outcomes. Only models at the $1km^2$ scale reliably reproduced observed dynamics and captured emergent population- and individual-level properties (Fig. 1F and S10). We conclude that the processes that regulate the size of outbreaks and overall prevalence of rabies, operate primarily on scales that are much smaller than those typically modelled for this disease.

Our modelling shows that epidemic growth is curtailed in two ways: from deaths of rabid dogs reducing contact opportunities, and through redundant exposures of dogs already incubating infection. These processes increasingly stem transmission in lower density areas where dogs have fewer contact opportunities (Fig. 4). Simulations of index infections to estimate R_0 (i.e., in an entirely susceptible population) show that rabid dogs bite, on average, 2.91 dogs leading to approximately 1.47 secondary cases per index case (95% Percentile Intervals (PI) 1.39-1.56). This R_0 value is slightly higher than previously estimated (5), in part due to population growth (median dog density increased from 12 to >20 dogs/km^2 over the 14 years) but varies across the landscape in relation to dog densities (Fig. 4) and according to how it is measured; estimates simulated from dogs sampled from the landscape (i.e., by grid cell, rather than in proportion to density) were slightly lower (1.35, 95% PI 1.27-1.43), whereas estimates from dogs sampled from the transmission network were slightly higher (1.48, 95% PI 1.38-1.58), as more cases occur in higher density grid cells (Fig. 4), [see (9)].

Under endemic circulation, the effective reproduction number, R, declines by just over 30% and remains near 1. Around 78% of this reduction is from recent rabies deaths removing potential contacts and 22% from re-exposures of already incubating dogs. Thus, infected dog movement (fig. S1) determines the scale of mechanisms that regulate endemic dynamics, such that even small outbreaks (~5 cases per square km) can result in substantive reductions in R, given the heterogeneous distribution of dogs on the landscape (Fig. 4). There remains ambiguity in the mechanisms underpinning density independent transmission at higher dog densities. Human responses likely play a role (45% of traced rabid dogs were either killed or tied), and are to some extent captured in our model, but these may operate differently during larger outbreaks (beyond those observed) and in more urbanised populations (<2% of dogs in this rural district live at

densities >100 dogs/km^2). Our data highlight how better understanding of functional responses, that describe theoretical relationships of transmission with density (10,11), are needed to predict endemic pathogen dynamics.

Individual variation in disease transmission causes rare but more explosive outbreaks and more frequent extinctions (13). We observed considerable variation in rabid dog behaviour (Fig. 1), with a few rabid dogs biting many others (4% of rabid dogs bit >10 other dogs each and four bit >50 dogs) and running long distances (nine rabid dogs ran >10 km to contact other animals). Overdispersion in the size of transmission chains (fig. S11) reflects this variability in rabid dog behaviour and thus makes persistence more remarkable (13). Our modelling captured this individual heterogeneity (Fig. 1F) revealing its importance in rabies dynamics: in counterfactual simulations without individual heterogeneity, rabies incidence was reduced by around 50% (fig. S7C) and the (relatively) large outbreaks observed in nature and in simulations with heterogeneity did not occur (Fig. 3C versus A). The biological drivers of this variation result predominantly from individual-level (13), rather than environmental or population-level differences (14, 15), such as host density, but are poorly understood. Behavioural manifestations of infection that depend on sociological and pathological factors, like exposure dose and sites of viral proliferation (16), might underpin this individual-level variation.

Both the scale of and heterogeneity in contact and movement are crucial to capturing rabies dynamics (Fig. 3). Density-dependent transmission processes, although well described theoretically (2, 17), are extremely challenging to quantify in relation to spatial scale. This may explain why few empirical studies of directly-transmitted diseases have found evidence of strong

density-dependent transmission (18–20). For rabies, the main susceptible depletion mechanisms - deaths of rabid dogs and re-exposures of dogs already incubating infection - only curtail transmission if infection is clustered and explain why non-spatial models of rabies do so poorly at replicating dynamics, since rabies incidence is negligible at the population-level. Clustering has been shown to reduce pathogen transmission via build-up of immune individuals (13), as well as in the context of redundant biting by insect vectors of disease (21); it has also been theorised to reduce transmission in the early stages of epidemics (22). For rabies, the incubation period acts in a similar way to immunity, resulting in redundant exposures that limit transmission. Natural immunity is not generally considered important in canine rabies or required to explain persistence, but antibodies have been detected in healthy unvaccinated dogs (17). If short-lived immunity does follow aborted infections, as may be the case for vampire bat rabies (18), our expectation is that it would cluster in the same way as incubating infections do, reinforcing local scale effects. Clustering has been demonstrated to make outbreaks less explosive and to extend persistence (19), yet the potential relevance of such micro-depletion mechanisms to many pathogens may be underestimated because their measurement relies on sufficiently resolved datasets. Our conclusion, that the relevant spatial scale at which to consider host density is determined by the scale of movements of infectious hosts, offers a starting point for the appropriate spatial scale at which to model other pathogens for which spatially detailed data are lacking.

Our analyses further illustrate the degree to which introduced cases contribute to rabies persistence. In the absence of introductions and under observed levels of vaccination, we expect infection to circulate in the Serengeti district for up to 7 years, typically dying out within 4 years (Fig. 3D). But, with between 8-24 rabid dogs arriving each year from neighbouring villages,

infection persists even under reasonable vaccination coverage, even though most cause only short-lived chains of transmission (fig. S10). In settings where vaccination coverage is negligible (i.e., dog populations across much of Africa and Asia), our simulations indicated a mean duration of outbreaks from single introductions of between 10-30 weeks; however, the maximum exceeded 12 years (fig. S10). Locally self-limiting clusters of cases recur on the landscape (Movie S1), and in combination with heterogeneous movement and contact, permit the invasion and co-circulation of multiple lineages (20) (Fig. 2). Recurrent introductions and extinctions have been reported in many endemic settings (21–23) and cross-border introductions have led to rabies emergence in several previously rabies-free areas (24–28). In contrast to diseases like mosquito-transmitted Dengue (29), chains of infection circulate largely independently, given the low prevalence of cases and very localised susceptible depletion. The concurrent extinction of all lineages therefore becomes less probable as more chains of infection co-circulate.

From a practical perspective, our findings explain why dog culling has typically been so ineffective for controlling rabies, since dog populations would need reducing below very low densities across all areas where infection is circulating. Indeed, culling over 50% of the 400,000 dogs in Flores, Indonesia, had no apparent impact on rabies circulation (30). Our results reinforce the message that mass dog vaccination remains the most effective and feasible method of controlling rabies and provides insights that should inform elimination strategies. Simulations indicate that while dog vaccinations prevented over 4,000 animal cases, 2,000 human rabies exposures and 50 deaths in the Serengeti district, introductions continually seeded new foci, with scaled up dog vaccination (beyond the district) required to achieve elimination (Fig. 3). Infrequent longer distance movements of rabid dogs seed outbreaks in unaffected localities across heterogeneously distributed populations, leading to localised flare-ups where vaccination

coverage is not maintained. The resulting low prevalence persistence presents a challenge for elimination given that surveillance is very weak in most rabies-endemic regions. Yet, the concurrent circulation of viral lineages offers an opportunity for using increasingly affordable genomic approaches to assess the performance of both rabies surveillance and control (31). Differentiating undetected circulation from reintroductions will be necessary as control efforts are scaled up towards the 2030 goal of zero human deaths from dog-mediated rabies (32).

References and Notes

1. H. McCallum, N. Barlow, J. Hone, How should pathogen transmission be modelled? Trends Ecol. Evol. 16, 295–300 (2001).

2. J. Lello, A. Fenton, Lost in transmission…? Philos. Trans. R. Soc. B Biol. Sci. 372, 20160082 (2017).

3. J. Jousimo, A. J. M. Tack, O. Ovaskainen, T. Mononen, H. Susi, C. Tollenaere, A.-L. Laine, Ecological and evolutionary effects of fragmentation on infectious disease dynamics. Science. 344, 1289–1293 (2014).

4. R. Anderson, R. May, Infectious Diseases of Humans: Dynamics and Control (Oxford University Press, 1991; https://global.oup.com/academic/product/infectious-diseases-of-humans-9780198540403?cc=gb&lang=en&).

5. K. Hampson, J. Dushoff, S. Cleaveland, D. T. Haydon, M. Kaare, C. Packer, A. Dobson, Transmission Dynamics and Prospects for the Elimination of Canine Rabies. PLOS Biol. 7, e1000053 (2009).

6. P. G. Coleman, C. Dye, Immunization coverage required to prevent outbreaks of dog rabies. Vaccine. 14, 185–186 (1996).

7. K. Hampson, L. Coudeville, T. Lembo, M. Sambo, A. Kieffer, M. Attlan, J. Barrat, J. D. Blanton, D. J. Briggs, S. Cleaveland, P. Costa, C. M. Freuling, E. Hiby, L. Knopf, F. Leanes, F.-X. Meslin, A. Metlin, M. E. Miranda, T. Müller, L. H. Nel, S. Recuenco, C. E. Rupprecht, C. Schumacher, L. Taylor, M. A. N. Vigilato, J. Zinsstag, J. Dushoff, on behalf of the G. A. for R. C. P. for R. Prevention, Estimating the Global Burden of Endemic Canine Rabies. PLoS Negl. Trop. Dis. 9, e0003709 (2015).

8. T. Lembo, K. Hampson, D. T. Haydon, M. Craft, A. Dobson, J. Dushoff, E. Ernest, R. Hoare, M. Kaare, T. Mlengeya, C. Mentzel, S. Cleaveland, Exploring reservoir dynamics: a case study of rabies in the Serengeti ecosystem. J. Appl. Ecol. 45, 1246–1257 (2008).

9. Materials and methods are available as supplementary materials.

10. A. M. Czupryna, J. S. Brown, M. A. Bigambo, C. J. Whelan, S. D. Mehta, R. M. Santymire, F. J. Lankester, L. J. Faust, Ecology and Demography of Free-Roaming Domestic Dogs in Rural Villages near Serengeti National Park in Tanzania. PLOS ONE. 11, e0167092 (2016).

11. C. S. Holling, The Components of Predation as Revealed by a Study of Small-Mammal Predation of the European Pine Sawfly1. Can. Entomol. 91, 293–320 (1959).

12. J. Antonovics, Y. Iwasa, M. P. Hassell, A Generalized Model of Parasitoid, Venereal, and Vector-Based Transmission Processes. Am. Nat. 145, 661–675 (1995).

13. J. O. Lloyd-Smith, S. J. Schreiber, P. E. Kopp, W. M. Getz, Superspreading and the effect of individual variation on disease emergence. Nature. 438, 355–359 (2005).

14. A. James, J. W. Pitchford, M. J. Plank, An event-based model of superspreading in epidemics. Proc. Biol. Sci. 274, 741–747 (2007).

15. O. Tardy, A. Massé, F. Pelletier, D. Fortin, Interplay between contact risk, conspecific density, and landscape connectivity: An individual-based modeling framework. Ecol. Model. 373, 25–38 (2018).

16. N. Mollentze, D. G. Streicker, P. R. Murcia, K. Hampson, R. Biek, Virulence mismatches in index hosts shape the outcomes of cross-species transmission. Proc. Natl. Acad. Sci. 117, 28859–28866 (2020).

17. S. Gold, C. A. Donnelly, P. Nouvellet, R. Woodroffe, Rabies virus-neutralising antibodies in healthy, unvaccinated individuals: What do they mean for rabies epidemiology? PLoS Negl. Trop. Dis. 14, e0007933 (2020).

18. J. C. Blackwood, D. G. Streicker, S. Altizer, P. Rohani, Resolving the roles of immunity, pathogenesis, and immigration for rabies persistence in vampire bats. Proc. Natl. Acad. Sci. 110, 20837–20842 (2013).

19. T. A. Perkins, T. W. Scott, A. L. Menach, D. L. Smith, Heterogeneity, Mixing, and the Spatial Scales of Mosquito-Borne Pathogen Transmission. PLOS Comput. Biol. 9, e1003327 (2013).

20. K. Brunker, P. Lemey, D. A. Marston, A. R. Fooks, A. Lugelo, C. Ngeleja, K. Hampson, R. Biek, Landscape attributes governing local transmission of an endemic zoonosis: Rabies virus in domestic dogs. Mol. Ecol. 27, 773–788 (2018).

21. H. Bourhy, E. Nakouné, M. Hall, P. Nouvellet, A. Lepelletier, C. Talbi, L. Watier, E. C. Holmes, S. Cauchemez, P. Lemey, C. A. Donnelly, A. Rambaut, Revealing the Micro-

scale Signature of Endemic Zoonotic Disease Transmission in an African Urban Setting. PLOS Pathog. 12, e1005525 (2016).

22. J. Zinsstag, M. Lechenne, M. Laager, R. Mindekem, S. Naïssengar, A. Oussiguéré, K. Bidjeh, G. Rives, J. Tessier, S. Madjaninan, M. Ouagal, D. D. Moto, I. O. Alfaroukh, Y. Muthiani, A. Traoré, J. Hattendorf, A. Lepelletier, L. Kergoat, H. Bourhy, L. Dacheux, T. Stadler, N. Chitnis, Vaccination of dogs in an African city interrupts rabies transmission and reduces human exposure. Sci. Transl. Med. 9 (2017), doi:10.1126/scitranslmed.aaf6984.

23. H. L. Beyer, K. Hampson, T. Lembo, S. Cleaveland, M. Kaare, D. T. Haydon, Metapopulation dynamics of rabies and the efficacy of vaccination. Proc. R. Soc. B Biol. Sci. 278, 2182–2190 (2011).

24. B. Sharma, N. K. Dhand, N. Timsina, M. P. Ward, Reemergence of Rabies in Chhukha District, Bhutan, 2008 - Volume 16, Number 12—December 2010 - Emerging Infectious Diseases journal - CDC, doi:10.3201/eid1612.100958.

25. K. Tohma, M. Saito, C. S. Demetria, D. L. Manalo, B. P. Quiambao, T. Kamigaki, H. Oshitani, Molecular and mathematical modeling analyses of inter-island transmission of rabies into a previously rabies-free island in the Philippines. Infect. Genet. Evol. 38, 22–28 (2016).

26. K. Rysava, T. Mancero, E. Caldas, M. F. de Carvalho, A. P. B. Castro, V. Gutiérrez, D. T. Haydon, P. C. D. Johnson, R. Mancy, L. R. Montebello, S. M. Rocha, J. F. Gonzalez Roldan, M. A. N. Vigilato, V. D. R. Vilas, K. Hampson, Towards the elimination of dog-mediated rabies: development and application of an evidence-based management tool. BMC Infect. Dis. 20, 778 (2020).

27. R. Castillo-Neyra, J. Brown, K. Borrini, C. Arevalo, M. Z. Levy, A. Buttenheim, G. C. Hunter, V. Becerra, J. Behrman, V. A. Paz-Soldan, Barriers to dog rabies vaccination during an urban rabies outbreak: Qualitative findings from Arequipa, Peru. PLoS Negl. Trop. Dis. 11, e0005460 (2017).

28. S. E. Townsend, I. P. Sumantra, Pudjiatmoko, G. N. Bagus, E. Brum, S. Cleaveland, S. Crafter, A. P. M. Dewi, D. M. N. Dharma, J. Dushoff, J. Girardi, I. K. Gunata, E. F. Hiby, C. Kalalo, D. L. Knobel, I. W. Mardiana, A. A. G. Putra, L. Schoonman, H. Scott–Orr, M. Shand, I. W. Sukanadi, P. P. Suseno, D. T. Haydon, K. Hampson, Designing Programs for Eliminating Canine Rabies from Islands: Bali, Indonesia as a Case Study. PLoS Negl. Trop. Dis. 7, e2372 (2013).

29. H. Salje, J. Lessler, I. M. Berry, M. C. Melendrez, T. Endy, S. Kalayanarooj, A. A-Nuegoonpipat, S. Chanama, S. Sangkijporn, C. Klungthong, B. Thaisomboonsuk, A. Nisalak, R. V. Gibbons, S. Iamsirithaworn, L. R. Macareo, I.-K. Yoon, A. Sangarsang, R. G. Jarman, D. A. T. Cummings, Dengue diversity across spatial and temporal scales: Local structure and the effect of host population size. Science. 355, 1302–1306 (2017).

30. C. Windiyaningsih, H. Wilde, F. X. Meslin, T. Suroso, H. S. Widarso, The rabies epidemic on Flores Island, Indonesia (1998-2003). J. Med. Assoc. Thail. Chotmaihet Thangphaet. 87, 1389–1393 (2004).

31. K. Brunker, G. Jaswant, S. M. Thumbi, K. Lushasi, A. Lugelo, A. M. Czupryna, F. Ade, G. Wambura, V. Chuchu, R. Steenson, C. Ngeleja, C. Bautista, D. L. Manalo, Ma. R. R. Gomez, M. Y. J. V. Chu, M. E. Miranda, M. Kamat, K. Rysava, J. Espineda, E. A. V. Silo, A. M. Aringo, R. P. Bernales, F. F. Adonay, M. J. Tildesley, D. A. Marston, D. L. Jennings, A. R. Fooks, W. Zhu, L. W. Meredith, S. C. Hill, R. Poplawski, R. J. Gifford, J.

B. Singer, M. Maturi, A. Mwatondo, R. Biek, K. Hampson, Rapid in-country sequencing of whole virus genomes to inform rabies elimination programmes. Wellcome Open Res. 5, 3 (2020).

32. R. Minghui, M. Stone, M. H. Semedo, L. Nel, New global strategic plan to eliminate dog-mediated rabies by 2030. Lancet Glob. Health. 6, e828–e829 (2018).

33. K. Hampson, boydorr/TransmissionScale: Zenodo release (v2.0). Zenodo. (2022), (available at https://doi.org/10.5281/zenodo.5885134).

34. National Bureau of Statistics, “Tanzania - Population and Housing Census 2012” (National Bureau of Statistics, Dar es Salaam, Tanzania, 2014), (available at https://www.nbs.go.tz/index.php/en/census-surveys/population-and-housing-census).

35. M. Hahsler, K. Hornik, TSP-Infrastructure for the Traveling Salesperson Problem. J. Stat. Softw. 23, 1–21 (2007).

36. A. Cori, P. Nouvellet, T. Garske, H. Bourhy, E. Nakouné, T. Jombart, A graph-based evidence synthesis approach to detecting outbreak clusters: An application to dog rabies. PLOS Comput. Biol. 14, e1006554 (2018).

37. M. Rajeev, mrajeev08/treerabid: Zenodo release (v1.0). Zenodo. (2021), (available at https://doi.org/10.5281/zenodo.5269062).

38. S. E. Townsend, T. Lembo, S. Cleaveland, F. X. Meslin, M. E. Miranda, A. A. G. Putra, D. T. Haydon, K. Hampson, Surveillance guidelines for disease elimination: A case study of canine rabies. Comp. Immunol. Microbiol. Infect. Dis. 36, 249–261 (2013).

39. J. Antonovics, Transmission dynamics: critical questions and challenges. Philos. Trans. R. Soc. B Biol. Sci. 372, 20160087 (2017).

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Supplementary Materials

Materials and Methods

Tables S1 to S2

Figs. S1 to S12

Movie S1

Fig. 1. Rabies in Serengeti district. (**A**) Mapped cases in red. Shading denotes dog density and lines village boundaries. The inset shows the district location in Tanzania. (**B**) Monthly time series of cases in domestic dogs (n=3,081, red) and other carnivores (grey, n=214; species detailed in *9*). (**C**) Dogs bitten per rabid dog versus dog density at each rabid dog's location ($1km^2$ scale), showed no apparent relationship (red line indicates the GAM prediction and grey lines the standard error, $p>0.05$). The inset shows the proportional distribution of the dog population and of case locations in relation to dog density on a logscale. Squares show mean dog population density (23 dogs/km^2, black) and mean dog density at case locations (41 dogs/km^2, red), indicating higher *per capita* incidence in higher density areas (independent samples t-test on log-transformed data, $T=22.45$, $p<2.2e-16$). Distributions of rabid dog (**D**) step-lengths

between contacts and distances to contacts (inset), (**E**) serial intervals and infectious periods (inset). The best-fitting distributions are shown in red (Table S1), with step-lengths and distances censored for animals with unknown starting locations (*9*). (**F**) Dogs bitten per rabid dog from contact tracing (grey) and simulated from the individual-based model (red, 5th to 95th percentiles). The y-axis is square root transformed in D and F to better illustrate extreme values.

Fig. 2. The spatiotemporal distribution of transmission chains. (A) Monthly cases (estimated to be between 83-95% of all cases in the district), highlighting in colour the 11 chains with most cases and all smaller chains (<58 cases) shaded grey, and **(B)** their spatial distribution, from the consensus tree of 1000 bootstrapped reconstructions (9).

Fig. 3. Time series of rabies cases and simulated counterfactual scenarios. Observed cases (red), with interquartile (dark shading) and 95% (light shading) prediction intervals, both computed pointwise, from simulations at the $1km^2$ scale, and with 3 illustrative example runs (dark lines). The simulated scenarios are: **(A)** with vaccination campaigns as implemented; **(B)** under low vaccination coverage; **(C)** with vaccination campaigns as implemented but no individual heterogeneity in contact parameters; and **(D)** without incursions after the first year.

Fig. 4. Rabies transmission in relation to population density. (**A**) Distribution of dog densities in Serengeti district on a log scale. (**B**) Holling curves computed from the most reliable parameter set at each scale *(9)*, with contact rate rescaled by the median infectious period (2 days) and dog density on a log scale; grey shading highlights dog densities below the median

(16.4 dogs per km^2) midway through the period (median density increased from 12 to 22 dogs/km^2 over the 14 years). The inset is replotted on a linear scale. At the optimal spatial scale (1km^2, red line) contact rates are density dependent at low dog densities and become increasingly density independent at higher densities. Parameter sets at other scales failed to reliably generate observed dynamics. The Holling curve indicates how even removal of a small number of susceptible dogs locally (from rabies deaths or incubating infection) reduces transmission such that R approaches 1 (corresponding to around 2 contacts per infection, horizontal line, with half developing rabies). (**C**) Histogram of R_0 estimates from simulating index infections (*9*), either by location (blue), density (orange) or from the transmission network (red). (**D**) Mapped R_0 estimates and (**E**) dog density at the midpoint.