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► To cite this version:

Jakob Zinsstag, Monique Lechenne, Mirjam Laager, Rolande Mindekem, Service Naïssengar, et al.. Vaccination of dogs in an African city interrupts rabies transmission and reduces human exposure. *Science Translational Medicine*, 2017, 9 (421), pp.eaaf6984. 10.1126/scitranslmed.aaf6984 . pasteur-03112653

HAL Id: pasteur-03112653

<https://pasteur.hal.science/pasteur-03112653>

Submitted on 17 Jan 2021

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Vaccination of dogs in an African city interrupts rabies transmission and reduces human exposure

Jakob Zinsstag^{1,2}, Monique Lechenne^{1,2}, Mirjam Laager^{1,2}, Rolande Mindekem³, Service Naïssengar⁴, Assandi Oussigéré⁴, Kebkiba Bidjeh⁴, Germain Rives^{1,2}, Julie Teissier^{1,2}, Seraphin Madjaninan³, Mahamat Ouagal⁴, Daugla D. Moto³, Idriss O. Alfaroukh⁴, Yvonne Muthiani^{1,2}, Abdallah Traoré⁵, Jan Hattendorf^{1,2}, Anthony Lepelletier⁶, Lauriane Kergoat⁶, Hervé Bourhy⁶, Laurent Dacheux⁶, Tanja Stadler^{7,8} Nakul Chitnis^{1,2}

¹Swiss Tropical and Public Health Institute, PO Box, 4002 Basel, Switzerland

²University of Basel, Petersplatz 1, 4003 Basel, Switzerland

³Centre de Support en Santé Internationale, BP 972, N'Djaména, Chad

⁴Institut de Recherches en Elevage pour le Développement, BP 433, N'Djaména, Chad

⁵Laboratoire Central Vétérinaire, BP2295, Bamako, Mali

⁶Institut Pasteur, Unit Lyssavirus Dynamics and Host Adaptation, WHO Collaborating Centre for Reference and Research on Rabies, 28 Rue du Docteur Roux, 75724 Paris Cedex 15, France

⁷Federal Institute of Technology (ETH), Department of Biosystems Science and Engineering, Mattenstrasse 26, 4058 Basel, Switzerland

⁸Swiss Institute of Bioinformatics, Lausanne, Switzerland

Overline: Epidemiology

24

25 **One sentence summary:** A citywide dog vaccination effort in Chad reduced the local
26 spread of rabies from dogs to humans.

27

28 **Abstract**

29 Despite the existence of effective rabies vaccines for dogs, dog transmitted human rabies persists
30 in Africa. Two consecutive dog vaccination campaigns in Chad in 2012 (dog vaccination
31 coverage: 72%) and 2013 (coverage: 70%) interrupted rabies transmission for nine months in
32 N'Djaména, the capital city. We developed a deterministic model of dog-human rabies
33 transmission fitted to weekly incidence data of rabid dogs and exposed human cases in
34 N'Djaména. Our analysis showed that the effective reproductive number, that is, the number of
35 new dogs infected by a rabid dog fell to below one through November 2014. The modeled
36 incidence of human rabies exposure fell to less than one person per million people per year. A
37 phylodynamic estimation of the effective reproductive number from 29 canine rabies virus
38 genetic sequences of the viral N-protein confirmed the results of the deterministic transmission
39 model, implying that rabies transmission was interrupted after the vaccination campaign.
40 However, new dog rabies cases appeared earlier than the transmission and phylodynamic models
41 predicted. This may have been due to the continuous movement of rabies-exposed dogs into
42 N'Djaména from outside the city. Our results show that canine rabies transmission to humans can
43 be interrupted in an African city with currently available dog rabies vaccines, provided the
44 vaccination area includes larger adjacent regions and local communities are informed and
45 engaged.

46

47 **Introduction**

48 Dog rabies has been eliminated in large parts of the industrialized countries in Europe and North
49 America. In the last few decades, a concerted effort by South and Central American countries has
50 reduced dog rabies transmission close to elimination (1). Despite the existence of effective
51 vaccines for dogs, dog transmitted human rabies persists and has even re-emerged in Asia and
52 Africa where still more than 59,000 people die annually from this preventable disease. The
53 largest part of the burden is borne by India followed by Africa, China and South East Asian
54 countries (2). Because of rabies' low propensity to transmit secondary infections beyond a bitten
55 individual, it appears feasible to eliminate dog-mediated human rabies through the mass
56 vaccination of dogs (3, 4). However, reaching this goal in partnership with the World Health
57 Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO), the
58 World Organization for Animal Health (OIE) and the Global Alliance for Rabies Control
59 (GARC, www.rabiesalliance.org) requires a rigorous scientific approach (5).

60

61 Reaching sufficient coverage to interrupt dog rabies virus transmission and prevent re-
62 introduction requires an in-depth understanding of dog ecology, dog-human interactions, and the
63 social and cultural determinants of vaccine acceptability, as well as the effective deployment of
64 vaccines with a highly sensitive surveillance system (4, 6-9). It requires scientists to closely
65 collaborate with authorities and communities as partners in a transdisciplinary way between
66 human and animal health (11, 12). Concomitant mathematical and economic frameworks can
67 yield new insights into fundamental properties of pathogen transmission (13) and comparative

68 cost-effectiveness (14) but do not explain sufficiently how this effectiveness can be achieved
69 (15).

70
71 In 2003, a smallscale study showed the feasibility of dog rabies control in an African city (6) with
72 low cost of US\$ 2-3 per vaccinated dog (16). However, in some African countries, dog owners
73 cannot afford anti-dog rabies inoculations and depend on mass vaccination campaigns that are
74 free of cost (8, 17). Analysis of pre- and post-vaccination rabies cases and economic data showed
75 that a single simulated dog vaccination campaign was able to interrupt transmission and was less
76 costly than human post-exposure prophylaxis (14). A proof of the feasibility of dog rabies
77 elimination in an African city would have far reaching consequences for a regionally concerted
78 effort to eliminate rabies in Africa.

79
80 A city-wide dog rabies mass vaccination campaign was set up in partnership with the Chadian
81 authorities, the Institut de Recherches en Elevage pour le Developpement (IRED), the Centre de
82 Support en Santé Internationale (CSSI) and the Swiss Tropical and Public Health Institute (Swiss
83 TPH)(23). The Chadian government paid for the costs of personnel and logistics and a
84 philanthropic donor paid for the costs of dog vaccines and research. Passive dog rabies and
85 human exposure surveillance started before the campaigns and is still ongoing. Here, we analyse
86 the passive surveillance data of dogs brought to the diagnostic laboratory from this prior work
87 using mathematical transmission models and phylodynamic analyses of dog-related rabies virus.
88 We investigate the impact of the vaccination campaigns for interrupting transmission and the
89 potential for maintaining elimination.

90

91 **Results**

92

93 **Mass vaccination and field data**

94 The vaccination campaign operations are described in detail in a previous publication (23) and
95 summarized in the materials and methods. Vaccination coverage surveys followed each sequence
96 to assess the achieved coverage and the deficit to reach 70% target coverage (23). In 2012, 72%
97 of all dogs were vaccinated (95% confidence interval 69-76%) and in 2013 70% were vaccinated
98 (95% confidence interval 69-75%).

99

100 Our results are based on data obtained about the weekly incidence of dogs newly infected with
101 rabies virus (Fig. 1A) and the incidence of related human exposure (Fig. 1B). These data were
102 collected through passive surveillance, i.e. by suspected dogs that were brought for testing to the
103 rabies laboratory in N'Djaména and through collection of rabies virus isolates from rabid dogs
104 throughout the vaccination campaign, described above. Recorded numbers of vaccinated dogs
105 were used for the estimation of vaccination coverage (23). These data were used to estimate the
106 effective reproductive number R_e (the number of new rabid dogs infected by one rabid dog at any
107 time, accounting for immunity and interventions, estimated from the transmission model) and the
108 threshold population density of susceptible dogs using mathematical models. The data suggested
109 that mass dog vaccination campaigns in 2012 and 2013 reached sufficient coverage to interrupt
110 rabies transmission from January 2014 to October 2014. Dog rabies incidence in the city of
111 N'Djaména, estimated from passive surveillance, dropped from 0.33 rabid dogs / (10 000*week)
112 prior to the mass vaccination campaign to 0.016 rabid dogs / (10 000 *week) in 2014 (Fig. 1A).
113 Similarly, the incidence of human exposure to rabid dogs, estimated from passive surveillance,

114 dropped from one human exposed to rabies virus / (1 000 000*week) prior to the mass
115 vaccination to less than 0.002 / (1 000 000*week) in 2014, which is less than one person per year
116 (Fig. 1B).

117

118 **Transmission model**

119 We used a deterministic, population-based model of ordinary differential equations to model
120 rabies virus transmission amongst dogs as well as between dogs and humans (Table S1). The
121 transmission model showed that between the two campaigns in 2012 and 2013, effective recorded
122 vaccination coverage decreased from a peak of 67% (December 2012) (23) to a trough of 33%
123 (October 2013), assuming an exponential distribution for the persistence of immunity, which was
124 estimated from 105 immunized dogs undergoing repeated serological measurements. This
125 represents a 51% relative coverage loss (Fig. 2A). The model suggested that population
126 replacement by the birth of susceptible dogs accounted for 29% of the relative coverage loss,
127 whereas individual dog immunity loss accounted for 22% of this relative coverage loss.

128

129 The effectively vaccinated surface area in our campaign of 240 km² (2012) was much lower than
130 the 770 km² assumed in an earlier simulation (14). The empirical data from this study provides a
131 better estimate of parameter values, the threshold density of susceptible dogs and the basic
132 reproductive number, i.e. the number of secondary infections resulting from a typical case in a
133 completely susceptible population, as $R_0 = 1.14$, instead of $R_0 = 1.01$. This means that rabies is
134 more infectious in N'Djaména, than previously reported (14). The effective reproductive number,
135 R_e , decreased from the equilibrium value of 1 from the start of the first vaccination campaign and
136 remained below 1 through November 2014, implying that the conditions for rabies virus
137 persistence were not maintained since the start of the vaccination campaigns. Simulations of a

138 deterministic ordinary differential equation model (Fig. 1), fitted to rabies case data from
139 N'Djaména, and a stochastic extension (Fig. 3) suggested that rabies transmission was interrupted
140 from early 2013 onwards.

141
142 As our model did not include importation of infections, we wondered whether dog rabies cases
143 seen from the October 2014 onwards (Fig. 1A) were due to imported cases (with subsequent
144 local transmission) rather than sustained ongoing transmission from the end of 2013 or the
145 beginning of 2014. To test this hypothesis, we performed a maximum likelihood phylogeny of
146 nucleoprotein sequences from rabies virus isolates collected in Chad (from N'Djaména and other
147 regions) from August 2011 to January 2015. Indeed, the dog rabies cases from 2014 onwards
148 were phylogenetically distinct from those previously circulating in N'Djaména (Fig. 4)). We
149 therefore suspected that domestic dogs from surrounding peri-urban and rural areas were the
150 more likely source of reinfection rather than ongoing transmission in dogs or wild animals.
151 Consistent with this, only dog-related rabies virus strains and no wildlife-related strains were
152 found in a previous rabies virus phylogenetic analysis performed in N'Djaména (19).

153

154

155 **Sensitivity analysis**

156 We performed sensitivity analysis to determine whether the simulation results were robust
157 compared to our estimates of parameter values. Figure S1 shows simulation results of the density
158 of infectious dogs over 6 years allowing for uncertainty in each of the parameter values (varied
159 one at a time). In each simulation run, the dog transmission rate, β_{dd} , was refitted for that set of
160 parameter values. The results were robust to uncertainty in the parameter values and except for
161 low vaccine efficacy values, the simulations predicted that transmission would be interrupted

162 after the first campaign. Fig. S2 shows a similar sensitivity analysis of the simulated number of
163 infectious dogs but with a fixed value for the dog transmission rate, β_{dd} , estimated from the
164 baseline set of parameter values (tableTS2). The ranges of the parameter values were greater than
165 in Fig. S1 and the results showed the importance of that parameter on the expected number of
166 rabid dogs over time. Most parameters had little effect, but similar to the sensitivity analysis for
167 R_c , high values for the carrying capacity of dogs and the probability of an exposed dog
168 developing rabies and low values for the rabies induced death rate led to a high number of
169 infectious dogs.

170
171 Fig. S3 shows the simulated densities of infectious dogs and exposed humans depending on the
172 probability of detection of infectious dogs, p_d , and of exposed humans, p_h , used to fit β_{dd} and
173 β_{hd} , respectively. Low values of these detection probabilities result in higher numbers of
174 infectious dogs and exposed humans, leading to higher estimates for the dog to dog, β_{dd} , and dog
175 to human, β_{hd} , transmission parameters. The results indicated that the simulation data were
176 robust regarding these detection probabilities unless the probabilities were very low and that
177 underreporting of rabies cases was unlikely to have a substantial effect on our results (Fig. S 3).
178 This in turn suggested that underreporting of cases did not play a large role in the persistence of
179 rabies transmission. Even accounting for heterogeneity in underreporting, it was unlikely that
180 unreported transmission persisted for nine months and more likely that a re-introduction
181 occurred, either from wildlife or from dogs with ongoing transmission outside the city of
182 N'Djaména.

183 **Phylodynamic analysis**

184 29 nucleotide sequences encoding the N-protein from dog related rabies virus isolates collected
185 between August 2011 and June 2013 were sequenced as previously described (9, 24). Although

186 the 95% highest posterior density intervals were wide because of the small number of sequences,
187 the effective reproductive number estimated from the genetic data showed the same pattern as
188 the R_e estimated from the incidence data (Fig. 2B). We demonstrate thus by two different
189 methods, transmission modelling and a phylodynamic analysis that dog rabies transmission can
190 be interrupted by the mass vaccination of dogs in N'Djaména.

191

192 **Discussion**

193 The models and data presented here show that the period with no rabies transmission in
194 N'Djaména was longer after mass vaccination campaigns than in the absence of such campaigns,
195 suggesting that dog rabies virus transmission in this African city could be interrupted and
196 consequently human rabies exposure reduced. However, the duration of interruption of
197 transmission in our study was shorter than our model predictions presented here and in earlier
198 work (14), indicating that there was likely to be a re-introduction of infection from wildlife or
199 latently infected dogs from the adjacent areas, similar to what was reported in a recent study on
200 rabies transmission in Bangui (26).

201

202 Our study suggested that urban centres may not be hotspots of dog rabies transmission leading to
203 spill over cases in rural areas, as previously thought. Dog rabies transmission is ongoing in peri-
204 urban and rural African areas and is likely to be continuously transmitted into urban areas
205 through human-mediated transport of dogs (9). Sustainable elimination of dog rabies therefore
206 will require action over a much larger geographical area. We have proposed a development
207 impact bond financing scheme for dog rabies elimination in the entire country of Chad (27).

208

209 There is still considerable uncertainty surrounding the role of density and spatial heterogeneity
210 and external re-introduction in the transmission of dog rabies (28). A meta-population or contact
211 network modeling approach may better represent the observed heterogeneity of the dog
212 population in N'Djaména (Fig. S4). Further research is needed to assess how dog density and the
213 spatial heterogeneity of dog populations influences the dynamics of dog rabies elimination (28,
214 29).

215
216 Determining the optimal timing of vaccination campaigns in N'Djaména to maintain elimination
217 would require better knowledge of the rabies importation rate into the city. Our results are in line
218 with a recent study from Bangui, Central African Republic showing that rabies is continuously
219 re-introduced in towns by human related transport of dogs from surrounding peri-urban and rural
220 areas (26) and rapidly dispersed between cities (9). Therefore, we suggest that dog rabies control
221 in African cities should be planned for larger areas, including suburban and rural areas, and be
222 coordinated regionally between neighboring countries for effective elimination of dog rabies in
223 Africa (1). In particular, movement of dogs with or without their owners should be restricted to
224 limit the rapid dispersal of dog associated rabies virus. Dog mass vaccination campaigns should
225 also be complemented by affordable compulsory dog registration. Our study further supports the
226 need for an improvement and a reinforcement of rabies surveillance in rural and more remote
227 areas to achieve inclusive and comprehensive rabies reporting that can then be used to guide
228 vaccination decisions. New rapid tests for rabies could be used in a decentralized manner and
229 may enable collection of data about rabies epidemiology in remote locations (30).

230
231 In contrast to previous reports (31), our study suggests that mass vaccination of dogs, coupled
232 with post-exposure prophylaxis, could be sufficient to eliminate rabies transmission in an

233 African city, both in dogs and humans, as long as vaccination is extended to a larger area beyond
234 the city itself. In the long term, eliminating the infectious rabies reservoir in dogs will be more
235 cost-effective than perpetual post or pre exposure prophylaxis in humans(32). Dog vaccination
236 campaigns will require a regional approach similar to the well-coordinated dog rabies control
237 efforts among Latin American countries (1). The recent creation of the Pan African Rabies
238 Control Network (PARACON, paracon.rabiesalliance.org) is an important first step towards the
239 goal of eliminating dog rabies from Africa by 2030.

240

241

242 **Supplementary materials**

243 **Supplementary Figures**

244 **Supplementary Figure 1:** 4 One -dimensional sensitivity analysis of simulation results on
245 parameter values. The plots show simulations of the density of infectious dogs over 6 years (300
246 weeks) where all parameters are fixed at values described in table S2 except for the parameter
247 being varied and β_{dd} . The x-axis shows the time in weeks and y-axis shows the value of the
248 parameter (in its corresponding units). The colour of each pixel represents the density of
249 infectious dogs. The horizontal red lines correspond to the parameter values in table S2 and the
250 solution plotted in Fig. 1A and Fig. 2A.

251

252 **Supplementary Figure 2:** One-dimensional sensitivity analysis of simulation results on parameter
253 values. The plots show simulations of the density of infectious dogs over 6 years (300 weeks)
254 where all parameters are fixed at values described in Table 3 except for the
255 parameter being varied (β_{dd} is fixed at 0.0292). The x-axis shows the time in weeks and y-

256 axis shows the value of the parameter (in its corresponding units). The colour of each pixel
257 represents the density of infectious dogs.

258
259 Supplementary Figure. 3: Sensitivity analysis of the simulation results on the probability of
260 detecting rabid dogs. (A) The simulated density of infectious dogs depending on the detection
261 probability of rabid dogs, p_d , over time. The x-axis corresponds to time (measured in weeks)
262 and the y-axis to the detection probability. The colour of each pixel corresponds to the density of
263 infectious dogs. (B) The endemic equilibrium value for density of infectious dogs (in the absence
264 of vaccination campaigns) depending on p_d . The x-axis corresponds to to the detection
265 probability, p_d and the y-axis (and colour of the pixel) correspond to the endemic equilibrium
266 density of infectious dogs.

267
268 Supplementary Figure. 4: Density of vaccinated dogs in N'Djaména in 2013 calculated based on
269 the data presented in Léchenne et al. 2016. Black dots indicate the locations of the fixed
270 vaccination posts. It is assumed that dogs diffuse from these locations after vaccination in a
271 homogeneous way. We used a diffusion kernel prediction map with a bandwidth of 1040 m
272 (which is the diameter of a circle of 0.86 km², the area per post of 331 posts in a total area of
273 285km²). The water surface was included as a barrier function.

274
275
276 Supplementary Figure. 5: Schematic of mathematical model of rabies. Birth and death rates of
277 humans and dogs are not shown.

278

279 Supplementary Figure 6: Vaccination rates during the two campaigns in N'Djaména, Chad a) in
280 2012 and b) in 2013. The weeks are labelled starting from 4 June 2012.

281
282 Supplementary Figure 7: Local and global sensitivity indices of the control reproductive number,
283 R_c , to the model parameters.

284
285 Supplementary Figure 8: Sample simulation of the stochastic model showing the density of
286 exposed and infectious dogs with the simulation results of the deterministic model and the
287 observed number of infectious dogs.

288
289 Supplementary Figure 9: Results of the phylodynamic analysis showing median (red) and 95%
290 HPD interval (black) for R_e through time. Solid lines correspond to the constant sampling
291 proportion assumption, and dashed lines to the changing sampling proportion assumption. Blue
292 points indicate the change of R_e and sampling proportion. We plot the R_e estimate for each
293 interval at the midpoint of the interval, and interpolate linearly in between.

294
295 Supplementary Tables

296 Supplementary Table 1: State variables of dog rabies transmission (model)

297
298 Supplementary Table 2. Parameters of the rabies transmission model with estimated values and
299 sources. Most parameters have the same value as in the previous model (14), but some have been
300 updated from more recent publications or from new data from the current study (as described in
301 the section on parameter estimation).

302

303 Data files

304 • RabiesData1.txt (incidence data)

305 • RabiesData2.txt (genetic sequences of 33 dog rabies virus N-protein deposited in GenBank)

306

307

308

309

310

311

312 **Materials and Methods**

313 **Study design**

314 The objective of this study was to test the hypotheses a) that dog rabies virus transmission in an

315 African city can be interrupted by the mass vaccination of dogs and b) that cities are hotspots of

316 dog rabies virus transmission and that re-introduction would be slow. As we observed the re-

317 introduction of dog rabies after the mass vaccination of dogs, we hypothesized that rabies virus

318 was re-introduced from the outside of the city. The research subjects were the weekly number

319 of routinely recorded rabies suspected dogs and the number of exposed humans per rabid dog.

320 The design of the present study is composed of four main components covering the city of

321 N'Djaména, Chad i): An ongoing passive dog rabies surveillance system. Suspected rabid dogs

322 (dead or alive) were brought to the rabies diagnostic laboratory. No active collection of

323 suspected dogs was done. For every rabies suspected dog, information on exposed humans was
324 collected on a routine basis. ii): A dog rabies mass vaccination campaign was done from October
325 to December 2012 and 2013 (23) Blood was taken from 104 dogs in 2012, prior to the start of
326 the mass vaccination campaign to assess the proportion of existing vaccination antibodies. The
327 Fluorescent antibody virus neutralization test (FAVN) was used for this purpose (33) . Data on
328 rabid dogs and exposed humans was collected up to the end of 2015 for this paper. iii) A
329 mathematical transmission model of dog to dog and dog to human rabies transmission was
330 parametrized from the weekly number of rabid dogs and exposed humans collected under i)
331 prior, during and after the mass vaccination campaign (ii). iv) A phylogenetic and phylo-dynamic
332 analysis of the rabies virus strains collected under i) was used to assess their genetic closeness
333 and to estimate the basic reproductive number of the rabies transmission in dogs independently
334 from the mathematical transmission model (iii).

335 **Surveillance of dog rabies and human exposure**

336 Passive routine dog rabies surveillance started on 4 June 2012 and is currently ongoing in
337 N'Djaména at the Institut de Recherches en Elevage pour le Développement by standard
338 immunofluorescence as described in (14, 18) . Prior to the mass vaccination campaign, the
339 average weekly incidence of dog rabies was of 0.33 dogs per 10,000. For every laboratory-
340 confirmed rabid dog, on average 1.6 humans were reported to be exposed (from questioning the
341 dog owner) leading to a weekly incidence of 0.11 per 100,000 people.

342

343 **Dog rabies mass vaccination campaign 2012 and 2013**

344 A citywide mass dog vaccination campaign including all 10 districts of N'Djaména took place in
345 2012 and was repeated in 2013. In both campaigns, the objective was to vaccinate 70% of the
346 total dog population of N'Djaména with the dog rabies vaccine RabisinTM (Merial Inc. Lyon,
347 France). The vaccination campaigns began in the first week of October 2012 and 2013 and lasted
348 for a total of 13 weeks until the first week of January of the next year. Vaccination took place
349 only on Friday to Sunday due to availability of staff and participation of the public during these
350 days (as evaluated in previous studies) (6). Every Friday to Sunday, ten fixed post vaccination
351 teams were set up in one of 12 (13 in 2013) areas of the city corresponding to administrative
352 boundaries. Over the three day period, these teams vaccinated on average 1,433 (min. 24; max.
353 6,460) dogs in 2012 and 1,709 dogs (min. 67; max. 4,591) dogs in 2013, depending on the socio-
354 cultural and ecological context of the city district (Table 1). Details of the operational
355 performance and the results of the vaccination campaigns are published elsewhere (23) .

356 **Coverage assessment**

357 A coverage assessment was carried out each week after vaccination in the previously vaccinated
358 area Fig. S4. Vaccination zones and their analysis perimeter corresponded in most cases to a
359 district. The coverage assessment was composed of a household survey in randomly selected
360 geographical locations within the analysis perimeter to estimate the proportion of owned
361 vaccinated dogs. In addition, random transects were carried out with a car in the same zone to
362 estimate the dog density in the street and the proportion of ownerless dogs. Data from both
363 studies were then combined in one Bayesian statistical model as reported elsewhere (23) .

364 **Description of mathematical model of dog-dog and dog-human** 365 **transmission**

366 We use a deterministic population based model of ordinary differential equations extended from a
 367 previously published model for dog to dog rabies transmission (14),

$$\frac{dS_d(t)}{dt} = b_d N_d(t) + \lambda_d V_d(t) - r_d \beta_{dd} S_d(t) I_d(t) - (v_d \alpha_d(t) + m_d + \gamma_d N_d(t)) S_d(t), \quad (1a)$$

$$\frac{dE_d(t)}{dt} = r_d \beta_{dd} S_d(t) I_d(t) - (\sigma_d + v_d \alpha_d(t) + m_d + \gamma_d N_d(t)) E_d(t), \quad (1b)$$

$$\frac{dI_d(t)}{dt} = \sigma_d E_d(t) - (\mu_d + m_d + \gamma_d N_d(t)) I_d(t), \quad (1c)$$

$$\frac{dV_d(t)}{dt} = v_d \alpha_d(t) (S_d(t) + E_d(t)) - (\lambda_d + m_d + \gamma_d N_d(t)) V_d(t), \quad (1d)$$

368 where the state variables and parameters are defined in Tables S1 and S2 respectively. The total
 369 dog population size is,

$$N_d(t) = S_d(t) + E_d(t) + I_d(t) + V_d(t), \quad (2)$$

370 and the density dependent death rate is,

$$\gamma_d = \frac{b_d - m_d}{K_d}, \quad (3)$$

371 where K_d is described in Table S2 and b_d is required to be greater than m_d . We note here that we
 372 assume density-dependent transmission and that in general, (1) is a non-autonomous model where
 373 $\alpha_d(t)$ varies with time,

$$\alpha_d(t) = \alpha_d^* + \alpha_0^{(i)}(t) + \alpha_1^{(i)}(t) e^{-\varphi t}, \quad (4)$$

374 where α_d^* is the (assumed) constant background vaccination rate, $\alpha_0^{(i)}(t)$ and $\alpha_1^{(i)}(t)$ are
 375 campaign-dependent vaccination values for the i^{th} week, and φ is a saturation parameter. Outside
 376 of the campaigns, $\alpha_d(t) = \alpha_d^*$. We further restrict the values of $\alpha_0^{(i)}$ and $\alpha_1^{(i)}$ to ensure that $\alpha_d(t)$
 377 is continuous so that the system for rabies transmission (1) has a unique solution that exists for all
 378 time.

379 We similarly use an ordinary differential equation model for dog to human transmission based on
 380 (14),

$$\frac{dS_h(t)}{dt} = b_h N_h(t) - \beta_{hd} S_h(t) I_d(t) + a_h E_h(t) - m_h S_h(t), \quad (5a)$$

$$\frac{dE_h(t)}{dt} = \beta_{hd} S_h(t) I_d(t) - (a_h + \sigma_h + m_h) E_h(t), \quad (5b)$$

$$\frac{dI_h(t)}{dt} = \sigma_h E_h(t) - (m_h + \mu_h) I_h(t), \quad (5c)$$

381 where the total human population size is,

$$N_h(t) = S_h(t) + E_h(t) + I_h(t), \quad (6)$$

382 σ_h is the rate of progression from the exposed to the infectious state depending on the site of the

383 bite,

$$\sigma_h = \frac{P_2 P_6}{i_{\text{head}}} + \frac{P_3 P_7}{i_{\text{arm}}} + \frac{P_4 P_8}{i_{\text{trunc}}} + \frac{P_5 P_9}{i_{\text{leg}}}, \quad (7)$$

384 a_h is the abortive rate of progression from the exposed back to the susceptible state,

$$a_h = \frac{P_2(1 - P_6)}{i_{\text{head}}} + \frac{P_3(1 - P_7)}{i_{\text{arm}}} + \frac{P_4(1 - P_8)}{i_{\text{trunc}}} + \frac{P_5(1 - P_9)}{i_{\text{leg}}}, \quad (8)$$

385 and the probabilities of biting different parts of the body (P_2 through P_5), the probabilities of

386 subsequent progression to rabies (P_6 through P_9), and the average time to do so ($1/i_\xi$ where ξ is

387 head, arm, trunk or leg), are described in more detail in the previous formulation of the model

388 (14). Fig. S5 shows a schematic of the model system. We note that the dynamics for rabies

389 transmission in humans is dependent on rabies transmission in dogs but the transmission in dogs

390 is independent of transmission in humans.

391

392 **Mathematical analysis**

393 In the absence of vaccination campaigns ($\alpha_d(t) = \alpha_d^*$), the autonomous mathematical model for

394 rabies transmission in dogs (1) has a trivial disease-free equilibrium point,

$$S_d = \frac{(b_d + \lambda_d)K_d}{b_d + \lambda_d + v_d\alpha_d^*}, \quad (9a)$$

$$E_d = 0, \quad (9b)$$

$$I_d = 0, \quad (9c)$$

$$V_d = \frac{v_d\alpha_d^*K_d}{b_d + \lambda_d + v_d\alpha_d^*}. \quad (9d)$$

395 The control reproductive number for the dog rabies model is the number of dogs that one newly
 396 introduced rabid dog would infect, assuming no disease in the population (with only background
 397 vaccination),

$$R_c = \frac{r_d\beta_{dd}\sigma_dK_d}{(\sigma_d + v_d\alpha_d^* + b_d)(\mu_d + b_d)}. \quad (10)$$

398 We omit the mathematical details here but can show that with only background vaccination (no
 399 vaccination campaigns) when $R_c < 1$, the disease-free equilibrium point (9) is locally
 400 asymptotically stable and when $R_c > 1$, the disease-free equilibrium point is unstable and there
 401 exists a locally asymptotically stable endemic equilibrium point where rabies persists in the
 402 population. Additionally, if there is no background vaccination, the control reproductive number
 403 reduces to the basic reproductive number,

$$R_0 = \frac{r_d\beta_{dd}\sigma_dK_d}{(\sigma_d + b_d)(\mu_d + b_d)}.$$

404 At any time, t , allowing for vaccination campaigns, the effective reproductive number, $R_e(t)$,
 405 represents the expected number of new infections caused by one infectious dog,

$$R_e(t) = \frac{r_d\beta_{dd}\sigma_dS_d(t)}{(\sigma_d + v_d\alpha_d(t) + m_d + \gamma_d N_d(t))(\mu_d + m_d + \gamma_d N_d(t))}.$$

407 (11)

408 If we assume that the total dog population is at carrying capacity (which is reasonable because
 409 the density of rabid dogs is low so has a minimal impact on the population density of dogs), the
 410 effective reproductive number simplifies to,

411
$$R_e(t) = \frac{r_d \beta_{dd} \sigma_d S_d(t)}{(\sigma_d + v_d \alpha_d(t) + b_d)(\mu_d + b_d)}. \quad (12)$$

412 The threshold density of susceptible dogs at which transmission occurs, S_d^* is the density at which

413 $R_e = 1$. From (12), outside of vaccination campaigns this is,

414
$$S_d^* = \frac{(\sigma_d + v_d \alpha_d^* + b_d)(\mu_d + b_d)}{r_d \beta_{dd} \sigma_d}. \quad (13)$$

415 The threshold vaccination coverage reached in a campaign to eliminate transmission, ψ^* , is given

416 by,

$$\psi^* = 1 - \frac{1}{R_c}, \quad (14)$$

417 when background vaccination takes place outside the campaign. Equivalently this is,

$$\psi^* = \frac{K_d - S_d^*}{K_d}. \quad (15)$$

418 After the vaccination campaigns, the coverage of protected dogs decreases exponentially due to

419 population loss of susceptible dogs (proportionally $b_d/(\lambda_d + b_d)$): 57% for parameter values in

420 table S2) and due to loss of vaccine efficacy (proportionally $\lambda_d/(\lambda_d + b_d)$): 43% for parameter

421 values in table S2).

422 **Parameter estimation**

423 The values for most parameters are taken from the previous model (14) except where new

424 published results or new data have allowed for revised values. The parameter values and their

425 sources are summarised in table S2. The birth and death rates of dogs were calculated as in

426 previous work but the carrying capacity of dogs was revised to reflect a total population of

427 25,103 dogs in an area of 240km² as estimated in the 2012 coverage assessment. The vaccination

428 rate of dogs and the transmission rates from dogs to dogs and dogs to humans were estimated as

429 described below.

430

431 **Dog vaccination rate**

432 The baseline study found that 12% (n=105) of all owned dogs had antibodies (and so could be
433 considered effectively vaccinated), implying that there was some ongoing background
434 vaccination outside of the two campaigns conducted in 2012 and 2013. The coverage assessment
435 estimated that for every 10 owned dogs, there was one unowned dog. Assuming that the
436 background vaccination rate was constant and the proportion of vaccinated dogs was at
437 equilibrium (9), with demographic and other vaccination parameters as in table S2, the per capita
438 background vaccination rate was 2.96×10^{-3} /week.

439 The number of dogs marked as vaccinated in each campaign is shown in Table 1. We estimated
440 the vaccination rate parameters, $\alpha_0^{(i)}$ and $\alpha_1^{(i)}$ using a simple model of vaccination for each
441 campaign,

$$\frac{dU^{(i)}}{dt} = b_d(K_d - U^{(i)}) - \bar{\alpha}_d^{(i)}(t)U^{(i)}, \quad (16a)$$

$$\frac{dV^{(i)}}{dt} = \bar{\alpha}_d^{(i)}(t)U^{(i)}, \quad (16b)$$

442 where $U^{(i)}$ is the density of all unmarked dogs, $V^{(i)}$ is the density of dogs marked in campaign
443 week i , and $\bar{\alpha}_d^{(i)}(t)$ is the rate of marking dogs during campaign week i . We define time, t , as
444 varying from 0 at the start of each campaign week to 1 at the end of each campaign week.

445 The coverage assessment could only determine whether dogs were marked as vaccinated or not
446 and did not determine the immune status of dogs. We therefore ignore the efficacy of the
447 vaccination and do not consider background vaccination because these dogs would not be marked
448 as campaign-vaccinated dogs, so

$$\bar{\alpha}_d^{(i)}(t) = \alpha_0^{(i)}(t) + \alpha_1^{(i)}(t)e^{-\varphi t}. \quad (17)$$

449 For simplicity we ignore rabies virus transmission, assume the dog population is at carrying
 450 capacity, and ignore the death of marked dogs or the loss of marking collars during the campaign
 451 week. Since the coverage assessment was conducted within three days of the vaccination
 452 campaign, these assumptions are reasonable. We assume that the markings from the 2012
 453 campaign do not last until 2013 so for both campaigns, the initial density of unmarked dogs is
 454 equal to the carrying capacity,

$$455 \quad U^{(1)}(0) = K_d,$$

$$456 \quad (18a)$$

457 and from continuity,

$$458 \quad U^{(i)}(0) = U^{(i-1)}(1) \quad \text{for } i > 1. \quad (18b)$$

459 The initial density of dogs marked during a campaign week is zero,

$$V^{(i)}(0) = 0 \quad \text{for } i \geq 1. \quad (18c)$$

460 We fix $\varphi = 100$. To ensure that $\alpha_d(t)$ is continuous, we set

$$\alpha_0^{(1)} + \alpha_1^{(1)} = 0, \quad (19a)$$

$$\alpha_0^{(i)} + \alpha_1^{(i)} = \alpha_0^{(i-1)} + \alpha_1^{(i-1)} e^{-\varphi} \quad \text{for } i > 1. \quad (19b)$$

461 The final density of dogs marked in a campaign week, $V^{(i)}(1)$ is set equal to the number of
 462 marked dogs estimated from the coverage assessment for that week (Table 1) divided by the
 463 campaign area for that year (240km² in 2012 and 285km² in 2013). Condition (19) and the
 464 ordinary differential equations for the vaccination model (16) with its boundary conditions
 465 provide two sets of equations for each campaign week. For other parameter values as provided in
 466 table S2, we numerically simulate the vaccination model using an adaptive step-size Runge-Kutta
 467 method (ode45) and then use a root-finding algorithm (fzero) to calculate $\alpha_0^{(i)}$ and $\alpha_1^{(i)}$ (in
 468 MATLAB, version 8.5) for each campaign week. Fig. S6 shows the final estimated vaccination
 469 rates during the two campaigns.

470

471 **Rate of loss of vaccine immunity**

472 In 2012, before the vaccination campaigns were conducted, a total of 105 dogs in N'Djaména
473 were tested for antibody titers, vaccinated and then followed up over a period of one year. Of
474 these dogs, 58 had initial antibody titers that showed no previous vaccination and were
475 successfully followed up over the entire year. After one year, 44 dogs had antibody titers above
476 0.5 IU, which, as a conservative estimate, we considered protective (34). We calculated the rate
477 of loss of vaccine decay, λ_d , assuming exponential decay and a relative value of 0.76 after 52
478 weeks.

479 **Rabies transmission rates**

480 The number of rabid dogs and exposed humans recorded per week since 4 June 2012 are shown
481 in the additional file RabiesData1.txt. Recording of both human and dog cases is ongoing but the
482 analysis only included cases until the end of October 2015. We divide the numbers of dogs and
483 humans by the area estimated in the coverage assessment of the 2012 vaccination campaign (240
484 km²) to provide the densities of rabid dogs and exposed humans.

485 We first fit the dog to dog transmission rate, β_{dd} , for the model with transmission only in dogs
486 (1) with the data for the number of rabid dogs with other parameter values as described in
487 table S2 and the vaccination rate as described above. We then use this value for β_{dd} to estimate
488 the dog to human transmission rate, β_{hd} , for the full model with transmission between dogs (1)
489 and to humans (5) with the data for number of exposed humans.

490 To fit β_{dd} , we numerically simulate (1) using an adaptive step-size Runge-Kutta method and
491 minimise the Euclidean distance between the simulated incidence of infectious dogs (from the
492 first term of the right hand side of (1c)), and the observed weekly incidence of infectious dogs in

493 MATLAB. We assume that the probability of detecting a rabid dog, $p_d = 0.5$ so that on average
494 there were twice as many rabid dogs as those detected. There is little data on this parameter but
495 our sensitivity analysis showed that unless p_d is very low, the estimated values for β_{dd} did not
496 change much (Fig. S3). We assume that the initial condition for the ordinary differential
497 equations in June 2012 is at the unique endemic equilibrium (with $\alpha_d(t) = \alpha_d^*$) and the dog
498 density is at carrying capacity.

499 We similarly fit β_{hd} by numerically simulating (1) and (5) and minimising the Euclidean distance
500 between the simulated density of exposed humans, $E_h(t)$, and the observed density of exposed
501 humans on a weekly time step in MATLAB. Here we assume perfect detection of exposed
502 humans ($p_h = 1$) and that the initial condition in June 2012 is at the unique endemic equilibrium
503 with a population density of humans of 4833 humans/km² (from a total population size of 1.16
504 million in 2012 estimated from the 2011 population size of 1.079 million using a growth rate of
505 7.5%) (35, 36).

506

507 **Phylogenetic importation analysis**

508 To investigate the hypothesis of a reintroduction of dog rabies virus in N'Djamena from outside
509 of the city after the vaccination campaigns, we performed a phylogenetic analysis using the
510 previously described 29 complete nucleoprotein sequences of rabies virus isolates collected
511 between August 2011 and January 2014, with the inclusion of one supplementary sequence of a
512 isolate collected during this period (GenBank accession number KY124541), in addition to the
513 sequences of the three first isolates collected in the city after this period (from February 2014 to
514 January 2015, GenBank accession numbers MF538629-31) and to published available sequences
515 from Chad (n=1) and from neighboring countries (n=14). Using jModelTest2 (37, 38), the best-fit
516 model of nucleotide substitution according to the Bayesian Information Criterion was the general

517 time reversible model with proportion of invariable sites plus gamma-distributed rate
518 heterogeneity (GTR+I+ Γ 4). A phylogenetic tree was then estimated using the maximum
519 likelihood (ML) method available in PhyML 3.0 (39) utilizing SPR branch-swapping. The
520 robustness of individual nodes on the phylogeny was estimated using 1,000 bootstrap replicates
521 and using the approximate likelihood ratio test (aLRT) with SH-like supports (40).

522

523 **Sensitivity analysis**

524 We conducted local and global sensitivity analysis of the control reproductive number, R_c , (10)
525 to the model parameters (Fig. S7). We used the normalized forward sensitivity index for the local
526 analysis (41, 42) at the parameter values defined in table S2 and the partial rank correlation
527 coefficients for the global analysis (43), assuming all parameters were uniformly distributed in
528 the intervals: $r_d \in [0.049, 1]$, $\beta_{dd} \in [0.00292, 0.0614]$, $K_d \in [10.5, 221]$, $\sigma_d \in$
529 $[0.0239, 0.504]$, $b_d \in [0.0013, 0.0273]$, $\mu_d \in [0.123, 2.59]$, $v_d \in [0.094, 1]$ and $\alpha_d^* \in$
530 $[0.000296, 0.00622]$. Both the local and global analysis showed that the probability of
531 developing rabies, r_d , the transmission rate, β_{dd} , the carrying capacity, K_d and the rabies virus
532 induced mortality rate, μ_d , had a strong impact on the threshold for sustained transmission, R_c ,
533 while the other parameters had minimal impact.

534

535

536 **Stochastic model simulations**

537 We derived and numerically simulated a stochastic dog to dog transmission model based on (1),
538 with the master equation,

$$\frac{dP(n, t)}{dt} = \sum_i [W_i(n|m_i)P(m_i, t) - W_i(m_i|n)P(n, t)], \quad (20)$$

539 where n is any state of the system at time t and W_i are the transmission rates deduced from the
 540 parameters in table S2, using the Gillespie algorithm with the tau-leaping simulation method (44,
 541 45) . Fig. S8 shows a sample stochastic simulation of the density of exposed and infectious dogs
 542 with the corresponding simulation of the deterministic model and the underlying data for the
 543 number of infectious dogs. Fig. 3B shows that the mean of 500 simulation runs of the stochastic
 544 model declines after the first vaccination campaign in a similar manner to the deterministic
 545 model.

546 **Phylodynamic analysis**

547 29 sequences of canine rabies viruses, collected between August 2011 and June 2013, were
 548 analysed with Beast v2 (25). We chose a Hasegawa-Kishino-Yano (HKY) model for substitutions
 549 with a relaxed log-normal clock (46). We assumed an exponential (0.001) prior for the mean
 550 rate, an exponential (0.3333) prior for the standard deviation, and a log-normal (1,1.25) prior
 551 for kappa.

552 For the epidemiological model, we chose the birth-death skyline model (47) . We used a log
 553 normal (0,1) prior for the effective reproductive number, R_e , and allowed R_e to change in
 554 January 2013, August 2012, and April 2012, i.e. every 4.8 months prior to the last sample in June
 555 2013. We assumed a uniform prior on the interval (9.44,9.5) for the dog removal rate
 556 (corresponding to an expected infection time of exposed and active rabies between (1/9.5,1/
 557 9.44) years, which is about 1.1 months. The sampling probability of a rabid dog was assumed to
 558 be 0 prior to the first sample, and uniform on (0.4,0.6) between the first and last sample. The
 559 time of the initial case in that transmission chain was assumed to be a uniform prior on (0,20),

560 prior to the most recent sample. We ran the Markov chain Monte Carlo (MCMC) simulations for
561 10^9 steps. We neglected the first 10% of the states as a burn-in period. The effective sample size
562 of all parameters was 350 or higher, implying that we obtained substantial mixing.

563 In order to investigate sensitivity towards our assumption of a constant sampling proportion, we
564 performed a second analysis allowing the sampling proportion to change at the same time points
565 as when the R_e changes. As above, sampling was assumed to be 0 prior to the oldest sample.

566 Further sampling was assumed to be uniform on (0.2,0.6) in each interval (compared to uniform
567 on (0.4,0.6) above. As shown in fig. S9 the results do not change qualitatively.

568

569 **Limitations of the study**

570 The study is limited by the low number of rabies viruses that were isolated during the rabies mass
571 vaccination campaign. For this reason, the credibility intervals of the phylodynamic estimation of
572 the basic reproductive number are wide. Another limitation is that we could not clearly identify
573 the source of the rabies viruses that were re-introduced from outside the city. Further ongoing
574 research will relate the rabies viruses collected in N'Djamena in this study with strains that will
575 be collected countrywide.

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717 233 (2013); published online EpubJan 2 (10.1073/pnas.1207965110).

718

719 **Acknowledgements:**

720 We thank all the community leaders and vaccinators in N'Djaména. We thank Thomas Smith for
721 helpful comments and discussions, and anonymous reviewers for helpful comments and
722 suggestions. There is no paid or unpaid consulting and there are no patents related to this work.

723

724 **Funding:**

725 Funding for this study was provided by the Chadian government, the UBS Optimus Foundation
726 and the Swiss Federal Food Safety and Veterinary Office (FFSVO), the European Union Seventh
727 Framework Programme PREDEMICS (grant #278433), the Wolfermann-Nägeli Foundation, the
728 Emilia Guggenheim Schnurr Foundation and the Swiss National Science Foundation (grant#:
729 310030_160067 / 1).

730 *Support was provided by the UBS Optimus Foundation (M.Le, R.M.), the Swiss Federal Food*
731 *Safety and Veterinary Office (FFSVO) (M.Le.), the Wolfermann-Nägeli Foundation (M.Le.),*
732 *Swiss Nationals Science foundation grant number 310030-160067 (M. La.),. and the European*
733 *Research Council under the Seventh Framework Programme of the European Commission*
734 *(PhyPD: grant agreement number 335529)(T.S.).*

735 *Requests for rabies virus strains require a Material Transfer Agreement and should be sent to*
736 *Service Naissengar Institut de Recherches en Elevage pour le Développement, BP 433,*
737 *N'Djaména, Chad email : naissengar@gmail.com*

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740 **Author contributions:**

741 J.Z.: conceived the study, J.Z. and I. A. O. applied for funding. J.Z., M. Le, M. La. J.H., A. L., H.
742 B., L. D., T.S., N.C. wrote the manuscript. M.Le., M.La., R.M., S.N., A.O., G.R., J.T., S.M.,
743 M.O., Y.M., A.T. participated in the acquisition and analysis of data. J. Z., M.La. N.C.
744 contributed to the mathematical modelling. S. N. did all the rabies diagnostic work. A.O.
745 coordinated the rabies mass vaccination campaign. J.Z., M. Le, M. La. A.O., K. B., M.O.,
746 D.D.M., I.A.O., Y.M., A.T. J. H., A.L., H. B., T.S., provided a substantial intellectual
747 contribution. K.B., J.T. D.D.M., I.A.O. provided administrative, technical or supervisory

748 support. D.D.M. took medical responsibility of the study A.L., L.K., H.B., L.D., participated in
749 the analysis of molecular genetic data of the rabies viruses. N.C.: Supervised the mathematical
750 modelling.

751 **Competing interests:**

752 None declared

753 **Data and materials availability:**

754 The dog and human rabies incidence data and the genetic sequences of 29 dog rabies virus N-
755 protein are available in the Supplementary materials. The N-protein sequences are deposited in
756 GenBank (<https://www.ncbi.nlm.nih.gov/nuccore/>) under the accession numbers KU564980-99
757 and KY124532-40.

- 758
- RabiesData1.txt (incidence data)
 - RabiesData2.txt (genetic sequences of 29 dog rabies virus N-protein deposited in GenBank)
- 759

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762 **Tables**

763
764 Table 1. Number of dogs vaccinated in each week of the vaccination campaigns. The campaign
765 in 2012 started on 8 October 2012 (week 19) and in 2013 started on 30 September 2013 (week
766 70), as described in (23).

767

Vaccination Week	Vaccinated dogs (2012)	Vaccinated dogs (2013)
1	834	722
2	181	468
3	376	330
4	24	434
5	793	67
6	2901	1173
7	6460	928
8	1393	4215
9	3074	4372
10	1698	3424
11	311	4591
12	385	979
13	209	525

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771 **Figures**

772 Fig. 1 (A) Cumulative incidence of dog rabies cases and human exposure. Cumulative incidence
773 of recorded cases of dog rabies (infectious dogs) and simulated incidence of dog rabies in
774 N'Djaména from 6 June 2012 to the end of October 2015. (B) Cumulative incidence of recorded
775 human exposure to rabid dogs and simulated incidence of human exposure to rabid dogs in
776 N'Djaména from 6 June 2012 to the end of October 2015.

777

778 Fig. 2 (A) Density of vaccinated and unvaccinated dogs in relation to the effective reproductive
779 number. Density of susceptible (blue lines) and vaccinated (red lines) dogs against time since 6
780 June 2012. The solid lines show the simulated values from an ordinary differential equation
781 transmission model from June 2012 to October 2015. (B) The effective reproductive number, R_e ,
782 and vaccination coverage against time. The solid red line shows the vaccination coverage and the
783 solid blue line shows the effective reproductive number – both estimated from the ordinary
784 differential equation transmission model. The black line is the median R_e obtained from the
785 phylogenetic sequencing data, with upper and lower 95% credible intervals as black dashed lines.

786 Fig. 3 (A) Stochastic simulations of the interruption of transmission. Distribution of the simulated
787 expected date of interruption of transmission from 1000 simulation runs of the stochastic model
788 of dog rabies virus transmission. (B) Mean and 90% credible interval for exposed and infectious
789 dogs from 500 runs of the stochastic model.

790

791 Fig. 4: Phylogeny of rabies viruses isolated during and after the mass vaccination campaign.

792 Maximum likelihood phylogeny of nucleoprotein sequences from rabies virus isolates collected

793 in Chad (from N'Djaména and other regions) from August 2011 to January 2015, and from
794 sequences of previous rabies virus isolates originated from Chad and from other neighboring
795 countries. Sequences in blue were obtained from isolates collected in N'Djaména, Chad, during
796 the period from August 2011 to January 2014, excepted for the sequences with an asterisk which
797 correspond to isolates collected outside of N'Djaména or without any precise origin (for one
798 isolate) during the same period. Sequences in red are those obtained from isolates collected in
799 N'Djaména from February 2014 to January 2015. Only bootstrap values > 70 are indicated on
800 selected nodes. A scale indicating genetic distance is presented by the horizontal bar. The tree is
801 mid-point rooted for clarity only. GenBank accession numbers of published sequences used in
802 this tree are: EU853590 (07072RCA), EU853651 (07149RCA), EU038107 (35RD8005),
803 KT119773 (8801CAM), KX148243 (8803CAM), U22635 (8804CAM), EU853654 (9014NIG),
804 KX148208 (92029CAR), KT119779 (9218TCH), KT119784 (9502CAM), KF977826
805 (CAR_11_001h), KC196743 (DRV_NG11), EU038108 (RD128), EU038096 (RD137) and
806 EU038093 (RD9305HN).

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