

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

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38

39 **Abstract**

40 **Background**

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

47 **Methodology & Principal Findings**

48 We use spatially resolved data on numbers of bite patients seeking PEP across
49 Madagascar and estimates of travel times to the closest clinic providing PEP ($N = 31$) in
50 a Bayesian regression framework to estimate how geographic access predicts reported
51 bite incidence. We find that travel times strongly predict reported bite incidence across
52 the country. Using resulting estimates in an adapted decision tree, we extrapolate
53 rabies deaths and reporting and find that geographic access to PEP shapes burden
54 sub-nationally. We estimate 960 human rabies deaths annually (95% Prediction
55 Intervals (PI): 790 - 1120), with PEP averting an additional 800 deaths (95% PI: 800
56 (95% PI: 640 - 970) each year. Under these assumptions, we find that expanding PEP
57 to one clinic per district (83 additional clinics) could reduce deaths by 19%, but even
58 with all major primary clinics provisioning PEP (1733 additional clinics), we still expect
59 substantial rabies mortality. Our quantitative estimates are most sensitive to

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65 assumptions of underlying rabies exposure incidence, but qualitative patterns of the
66 impacts of travel times and expanded PEP access are robust.

67 **Conclusions & Significance**

68 PEP is effective at preventing rabies deaths, and in the absence of strong surveillance,
69 targeting underserved populations may be the most equitable way to provision PEP.

70 Given the potential for countries to use Gavi funding to expand access to PEP in the Deleted: Our
71 coming years, this framework could be used as a first step to guide expansion and Deleted: PEP
72 improve targeting of interventions in similar endemic settings where PEP access is
73 geographically restricted, and baseline data on rabies risk is lacking. While better PEP Deleted: .
74 access should save many lives, improved outreach, surveillance, and dog vaccination Deleted: and
75 will be necessary, and if rolled out with Gavi investment, could catalyze progress Deleted: is needed
76 towards achieving zero rabies deaths.

77 **Author Summary**

78 Canine rabies causes an estimated 60,000 deaths each year across the world, primarily
79 in low- and middle-income countries where people have limited access to both human
80 vaccines (post-exposure prophylaxis or PEP) and dog rabies vaccines. Given that we
81 have the tools to prevent rabies deaths, a global target has been set to eliminate deaths
82 due to canine rabies by 2030, and recently, Gavi, a multilateral organization that aims to
83 improve access to vaccines in the poorest countries, added human rabies vaccine to its
84 portfolio. In this study, we estimated reported incidence of patients seeking PEP in Deleted: bite
85 relation to travel times to clinics provisioning PEP, and extrapolate human rabies deaths Deleted: ,

93 in Madagascar. We find that PEP currently averts around 800 deaths each year, but
94 that the burden remains high (1000 deaths/ year), particularly in remote, hard-to-reach
95 areas. We show that expanding PEP availability to more clinics could significantly
96 reduce rabies deaths in Madagascar, but our results reaffirm that expansion alone is will
97 not achieve the global goal of zero human deaths from dog-mediated rabies by 2030.

98 Combining PEP expansion with outreach, surveillance, and mass dog vaccination
99 programs will be necessary to move Madagascar, and other Low- and Middle-Income
100 countries, forward on the path to rabies elimination.

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104 **Introduction**

105 Inequities in access to care are a major driver of disease burden globally [1]. Often, the
106 populations at greatest risk of a given disease are the most underserved [2]. Delivering
107 interventions to these groups is challenging due to financial and infrastructural
108 limitations and requires careful consideration of how best to allocate limited resources
109 [3].

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

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118 In 2015, a global framework to eliminate deaths due to canine rabies by 2030 ('Zero by
119 30') through a combination of PEP provisioning and dog vaccination was established by
120 the World Health Organization (WHO) and partners [10]. Furthermore, in 2018, Gavi,
121 the Vaccine Alliance, added human rabies vaccines to their proposed investment
122 portfolio [11]. From 2021, Gavi-eligible countries should be able to apply for support to
123 expand access to these vaccines, with potential to greatly reduce deaths due to rabies.
124 A primary challenge in expanding access effectively is the lack of data on rabies
125 exposures and deaths in humans and incidence in animals in most rabies-endemic

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

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

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154 apply to other countries where PEP availability is currently geographically restricted in
155 considering how to most effectively and equitably provision these life-saving vaccines.

156 Methods

157 Estimating geographic access to PEP

158 To estimate mean and population weighted travel times to the nearest clinic, we used
159 two raster datasets: 1) the friction surface from the Malaria Atlas Project [18] at an ~1
160 km² scale (Fig S1.1A) and 2) the population estimates from the 2015 UN adjusted
161 population projections from World Pop ([19], originally at an ~100m² resolution, Fig
162 S1.1B), which we aggregated to the friction surface.

163 From GPS locations of the 31 clinics that currently provision PEP, we estimated the
164 travel time to the nearest clinic at an approximately 1 x 1 km scale as described in [18].

165 We then extracted the mean and population-weighted mean travel times for each district
166 (2nd level administrative division, N = 114) and commune (the administrative unit below
167 the district, N = 1579), and Euclidean distance, i.e. the minimum distance from the
168 administrative unit centroid to any clinic. We used shapefiles from the UN Office for the
169 Coordination of Humanitarian Affairs for the district and communes boundaries (as of
170 October 31, 2018). To see which metric best predicted ground-truthed travel time data,
171 we compared travel times and distance estimates to driving times collected by IPM
172 during field missions, i.e. time it took to travel by car between two locations excluding
173 break times (N = nrow(ttime_driving)), and patient reported travel times from a subset

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186 of Moramanga clinic bite patients (N = 1057), see Fig S1.2 for raw data) by seeing
187 which worked best to predict estimated travel times in a linear model.

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188 Estimating bite incidence

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

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- 190 • A national database of individual bite patient forms from the 31 clinics provisioning
191 PEP across the country between 2014 - 2017. These forms were submitted to IPM
192 with frequencies ranging from monthly to annually, included the patient reporting
193 date and were resolved to the district level (patient residence).
- 194 • 33 months of data (between October 2016 and June 2019) on patients reporting to
195 the Moramanga clinic resolved to the commune level.

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

214 in a catchment of a clinic which submitted less than 10 forms and any years for which
215 we estimated less than 25% of forms were submitted.

216 **Modeling reported bite incidence as a function of access**

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

219
$$\mu_i = e^{(\beta_t T_i + \beta_0)} P_i$$

220
$$y_i = Poisson(\mu_i)$$

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

228
$$\mu_i = \sum_j^j e^{(\beta_t T_j + \beta_{0j})} P_j$$

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

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

238 We tested whether the catchment random effect captured overdispersion in the data
239 (i.e. variance > mean – the expectation given a Poisson distribution) rather than any
240 catchment specific effects by extending these models with an overdispersion parameter:
241 $\epsilon_i \sim \text{norm}(0, \sigma_e)$, where σ_e is the standard deviation around a random variable with
242 mean of zero [20]:

243
$$\mu_i = e^{(\sum_{j=1}^J \beta_j X_j + \epsilon_i)} P_i$$

244 where $\sum_{j=1}^J \beta_j X_j$ is the sum of the all parameters for a given model. We fit all models in
245 a Bayesian regression framework via MCMC using the R package ‘rjags’ [21]. We used
246 model estimates to generate fitted and out-of-fit predictions, and examined the
247 sensitivity of estimates to adjustments for under-submission of forms (Supplementary
248 Appendix, section S3).

249 Modeling human rabies deaths

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

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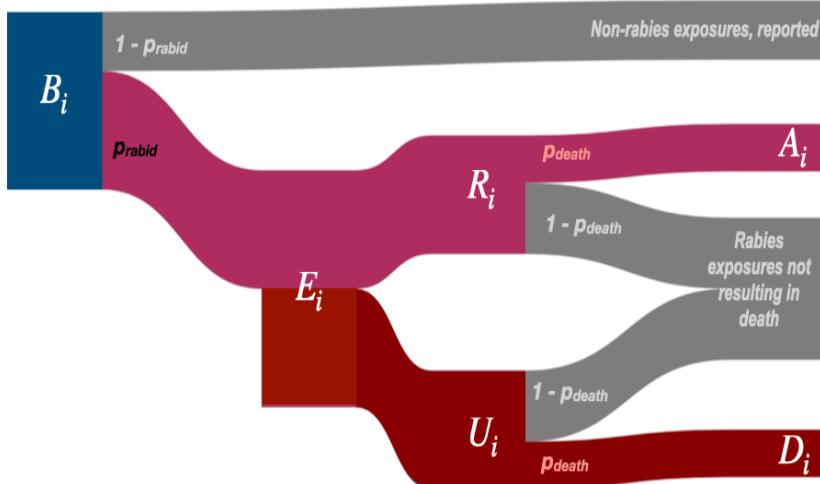
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Deleted: (Fig 1). To model uncertainty in parameter estimates we used triangular distributions, as with previous studies [8,22], for two key parameters: E_i , the annual exposure incidence per administrative unit, and p_{rabid} , the proportion of reported bites that are rabies exposures.

263 [Table 1. Parameters used in the decision tree to estimate human rabies deaths at](#)
 264 [the administrative level.](#)

<u>Parameter</u>	<u>Value</u>	<u>Description</u>	<u>Source</u>
B_i	Function of travel time to closest clinic provisioning PEP	Modeled estimates of reported bite incidence	Bayesian regression model (see Methods)
E_i	Triangular(a = 15, b = 76, c = 42)	Annual exposures per 100,000 persons	[4,15], see Fig S4.1
p_{rabid}	Triangular(a = 0.2, b = 0.6, c = 0.4)	Proportion of reported bites that are rabies exposures ¹	[15]
ρ_{max}	0.98	The maximum reporting possible for any location; data from the commune closest to the Moramanga PEP clinic (average of 3.12 minutes travel time to the clinic)	[15]
p_{death}	0.16	The probability of death given a rabies exposure	[22]

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



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269 **Fig 1. Decision tree for burden estimation.**

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

Deleted: p_{rabid} is constrained such that reported rabies exposures cannot exceed total rabies exposures (E_i) and reporting of patients to clinics cannot exceed a maximum (p_{max}).

283 For E_i , we center the distribution at the lower end of our estimated exposure incidence
 284 from the Moramanga District (42 exposures/100,000 persons), with a range applied
 285 assuming 1% rabies incidence in dogs (estimated across a range of human-to-dog
 286 ratios between 5 - 25) and that on average a rabid dog exposes 0.39 persons [4] (see
 287 Fig S4.1). As there is little data on dog population size and human exposure incidence
 288 in Madagascar[16,23], the range we used encompasses both observed human-to-dog
 289 ratios across Africa [14,24] and recent subnational estimates from Madagascar [25],
 290 and generates similar exposure incidences as observed previously across Africa
 291 [26,27]. Given previously high observed compliance in Madagascar [15], we assume
 292 that all rabies exposed patients who report to a clinic receive and complete PEP, and
 293 PEP is completely effective at preventing rabies.

295 Estimating the impact of expanding PEP provisioning

296 We developed a framework to rank clinics by how much their PEP provision improves
 297 access for underserved communities, estimating incremental reductions in burden and
 298 increases in vaccine demand. Specifically, we aggregated our model-predicted
 299 estimates of annual bites to the clinic level. As multiple clinics may serve a single district
 300 or commune, we allocated bites to clinics according to the proportion of the population
 301 in each administrative unit which were closest. For each clinic, we simulate throughput
 302 by randomly assigning patient presentation dates, and then assume perfect compliance
 303 (i.e. patients report for all doses) to generate subsequent vaccination dates. We use
 304 these dates to estimate vial usage given routine vial sharing practices in Madagascar
 305 [15], but assuming adoption of the WHO-recommended abridged intradermal regimen

Deleted: For p_{rabid} , we use a range between 0.2 - 0.6 estimated from a study of bite patients in the Moramanga District [15]. So that rabid reported bites cannot exceed the total expected number of rabies exposures or a maximum reporting (even with minimal travel times, people may not report for PEP for other reasons), we constrain p_{rabid} ¶

$$p_{rabid} = \begin{cases} x, & \text{if } \frac{E_i \rho_{max}}{B_i} > x \\ \frac{E_i \rho_{max}}{B_i}, & \text{otherwise} \end{cases} ¶$$

where ρ_{max} is the maximum reporting, estimated from the Moramanga ARMC data for the commune of Moramanga Ville, the closest commune to the ARMC (average of 3.12 minutes travel time to the clinic), and where we find that approximately 2% of rabies exposures go unreported [15].¶

We assume that all rabies exposed patients who report to an ARMC receive and complete PEP, and PEP is completely effective at preventing rabies. Fig 1 describes the decision tree, the key inputs, and outputs (A_i , deaths averted by PEP, and D_i , deaths due to rabies). Table 1 list all inputs and their sources.¶

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

Parameter ... [1]

331 (2 x 0.1 ml injections on days 0, 3, and 7 [28]). For both burden and vial estimates, we
332 take the mean of 1000 simulations as each clinic is added.

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333 We simulate expansion first to each district (N = 114) and then to each commune in the
334 country for all communes with a clinic. We select the primary clinic (primary health
335 facility, usually with capacity to provision vaccines) in the highest density grid cell of the
336 administrative unit as candidates for expansion. For the 85 communes without a primary
337 clinic, we chose the secondary clinic (secondary health facility, often without formal
338 vaccination capacity) in the highest density grid cell. 94 communes lacked any health
339 facilities. Finally, we explore a scenario where all additional primary clinics (totaling
340 1733) provision PEP.

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341 We tested three metrics for ranking additional clinics: 1) The proportion of people living
342 >3 hours from a existing PEP clinic that provisions PEP for which travel times were
343 reduced; 2) This proportion (1), weighted by the magnitude of the change in travel times
344 and 3) The mean reduction in travel times for people living >3 hours from an existing
345 PEP clinic. We simulated expansion of clinics provisioning PEP to each district using
346 these three metrics and chose the metric which decreased burden the most compared
347 to simulations (N = 10) where clinics were added randomly to districts for the full
348 expansion of PEP. For the full simulation of expanded access, once clinics reduced
349 travel times for less than 0.01% of the population (< 2400 living greater than x hrs away,
350 starting with x = 3 hrs), we reduced the travel time threshold by 25%.

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365 **Sensitivity analysis**

366 To test the effect of our model assumptions on estimates of rabies burden and vial
367 demand, we did a univariate sensitivity analysis of both parameters from the models of
368 bite incidence and the decision tree (see Table S6.1 & S6.2 for parameter ranges used).
369 We also examined how systematic variation in rabies incidence with human population
370 size affected burden estimates. Specifically, if human-to-dog ratios are positively
371 correlated with human populations (i.e. dog ownership/populations are higher in more
372 populated, urban areas), we might expect higher rabies exposure incidence as
373 population size increases. Alternatively, if human-to-dog ratios inversely correlate with
374 population size (i.e. dog ownership is more common in less populated, rural areas), we
375 might expect exposure incidence to scale negatively with population size. We use
376 scaling factors to scale incidence either positively or negatively with observed
377 population sizes at the district and commune levels, while constraining them to the
378 range of exposure incidence used in the main analyses (15.6 - 76 exposures per
379 100,000 persons, Fig S4.2) and simulated baseline burden, as well as expanded PEP
380 access.

381 **Data and analyses**

382 All analyses were done in R version 4.0.2 (2020-06-22) [29] and using the packages
383 listed in the supplementary references (Supplementary appendix, section S7). All
384 processed data, code, and outputs are archived on Zenodo
385 (<http://doi.org/10.5281/zenodo.4064312> and <https://doi.org/10.5281/zenodo.4064304>),
386 and maintained at <https://github.com/mrajeev08/MadaAccess>. The raw bite patient data

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388 at the national level are maintained in two secure REDCap (project-redcap.org)
389 databases, one for IPM and another for all peripheral clinics provisioning PEP. These
390 databases were last queried on September 19, 2019 for these analyses. The IPM GIS
391 unit provided the data on geolocated clinics across the country. Anonymized raw bite
392 patient data and full data on geolocated clinics are available from IPM following
393 institutional data transfer protocols. Anonymized raw data collected from the
394 Moramanga District were retrieved from the Wise Monkey Portal
395 (wisemonkeyfoundation.org) on the same date and are shared in the archived
396 repository.

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397 Ethics statement

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

403 Results

404 Estimates of travel times to clinics are high and variable across Madagascar.
405 Based on the estimates from the friction surface, approximately 36% of the population
406 of Madagascar are estimated to live over 3 hours from a clinic (Fig 2). However, we
407 found that these estimates underestimated both driving times across the country and
408 patient-reported travel times to the Moramanga PEP clinic (Fig 2C). Patient reported

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421 travel times were highly variable for a given commune compared to the estimated travel

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422 times (Fig S1.2), potentially due to the fact that the friction surface assumes that the

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423 fastest available mode of transport is used across each grid cell (i.e. the presence of a

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424 road indicates that all travel through that grid cell is by vehicle). However, patients

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425 reported using multiple modes of transport, with some individuals walking days to the

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426 Moramanga PEP clinic (Fig S1.3).

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427 While the travel time estimates may not reflect exact distributions of travel times, they

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428 were correlated with ground-truthed driving and patient-reported times and likely reflect

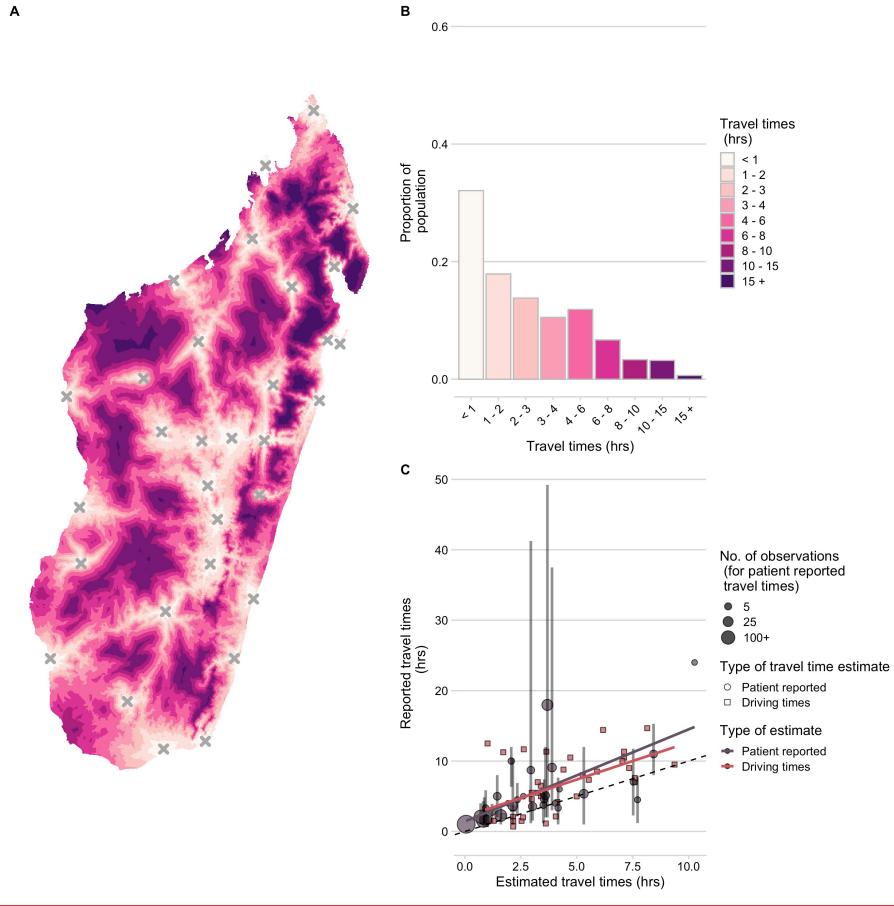
429 patterns of access over the country (Fig 3C, Fig S1.4). Travel times weighted by

430 population at the grid cell level were a better predictor than unweighted travel times or

431 distance ($R^2 = 0.43$, Table S1.1), therefore, we use population-weighted travel time as a

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432 proxy for access at the commune/district level in subsequent analyses.



440
441 **Fig 2. Travel times to clinics provisioning PEP across Madagascar.**

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442 (A) Estimated at an ~ 1 km² scale. (B) Distribution of the population across travel times.
 443 (C) Correlation between ground-truthed travel times (mean of patient reported travel
 444 times to the Moramanga PEP clinic at the commune level and reported driving times
 445 between GPS points) and friction surface travel time estimates. The vertical lines show

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448 the 95% quantiles for reported travel times and the point size shows the number of
449 observations for each commune. The best fit lines (red and grey) from a linear model
450 where observed travel times are predicted by estimated travel times for each data
451 source are also shown. The dashed black line is the 1:1 line.

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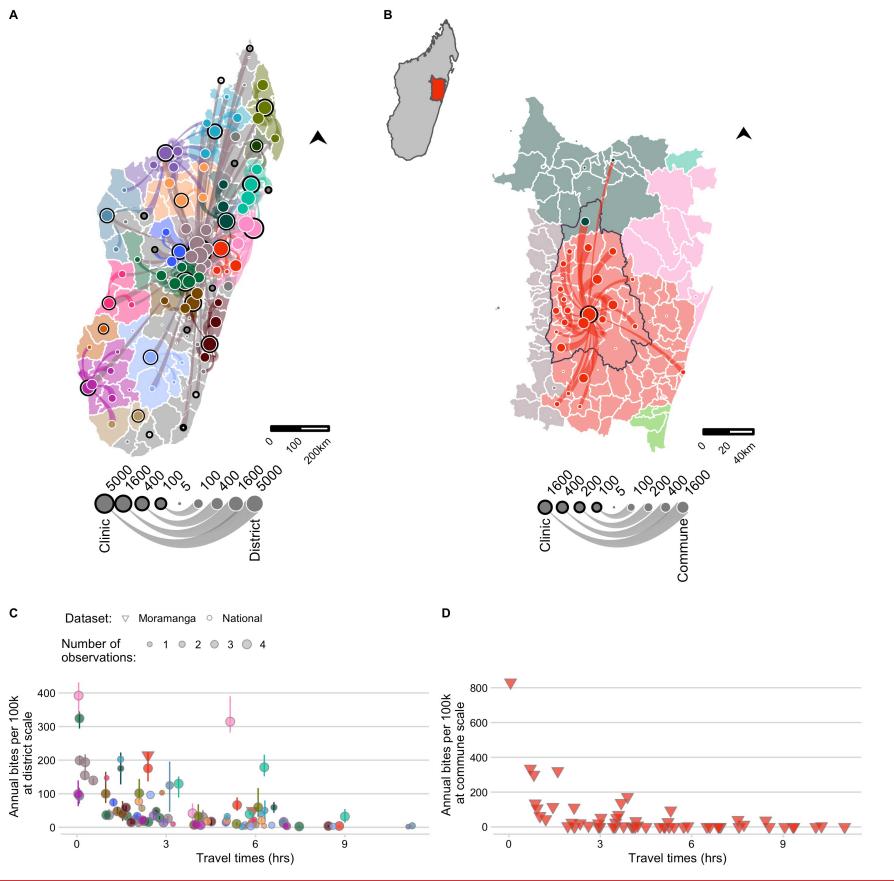
452 **As travel times increase, reported bite incidence decreases.**

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

Deleted: Most patients from each district reported to their closest ARMC by the weighted travel time metric (Fig 3). Accordingly, we assigned catchments based on which clinic was the closest for the majority of the population. While there are discrepancies between commune and district catchment assignments (Fig S2.1A), over 75% of the population in a given district or commune were closest to a single clinic (Fig S2.1C). We excluded any clinics which submitted less than 10 forms (excluded 11 catchments, Fig 3A grey polygons) and corrected for periods where clinics did not submit any forms (see Supplementary Appendix Section S2).

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488 white outline are the total number of bites reported for that administrative unit (plotted as
489 the centroid). Lines show which clinic those patients reported to, with the line width
490 proportional to number of patients from that district reporting to the clinic; flows of less
491 than 5 patients were excluded. Out-of-catchment reporting is indicated where points and
492 line colors are mismatched. For panel (A) districts in catchments excluded due to lack of
493 forms submitted by the clinic are colored in grey. For (B) the inset of Madagascar shows
494 the location of the enlarged area plotted, which shows the district of Moramanga
495 (outlined in black), all communes included in its catchment (red polygons), and other
496 communes where bites were reported to colored by their catchment (C) The estimated
497 average annual bite incidence from the national and Moramanga data plotted at the
498 district scale (both datasets) and at the (D) commune scale (Moramanga dataset).
499 Colors correspond to the clinic catchment, shape indicates the dataset, and the size of
500 the point indicates the number of observations (i.e. the number of years for which data
501 was available for the national data; note for Moramanga 33 months of data were used).
502 The point lines indicate the range of estimated bite incidence for each district.

503 Our modeling results show that travel times were a strong and consistent predictor of
504 reported bite incidence in both datasets and across scales with the best fitting models
505 including travel times and an overdispersion parameter (Fig 4, see Supplementary
506 Appendix section S3 for comparisons to models with catchment effects and with
507 population size as a covariate). As the predictions of the model fit to the Moramanga
508 data without accounting for overdispersion fall within the prediction intervals for the
509 models fit to the national data (Fig 4A), for subsequent predictions, we used the
510 parameter estimates from models fit to the national data, which encompass the range of

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Deleted: Bite incidence estimates generally increased with decreasing weighted travel times at both scales, although there was considerable variation between catchments for the magnitude of this relationship (Fig 3C and D). For the national data, there were two outliers, Toamasina II (the sub-urban district surrounding the city of Toamasina) and Soanierana Ivongo, with higher bite incidence when compared to other districts with similar travel times. While the estimates from the Moramanga data showed higher reported incidence at low travel times at the commune level compared to the district estimates, when aggregated to the district, bite incidence estimates fell within the ranges observed from the national dataset. [Modeling reported bite incidence](#) [Travel](#)

Deleted: (Fig 4). Population size alone was

Deleted: poorest fit to the data as estimated by DIC (Table S3.1), and

Deleted: with population size as an additional covariate did not generate realistic predictions to the observed data or when used to predict out of fit (Figs S3.2 and S3.3). [For the national data,](#)

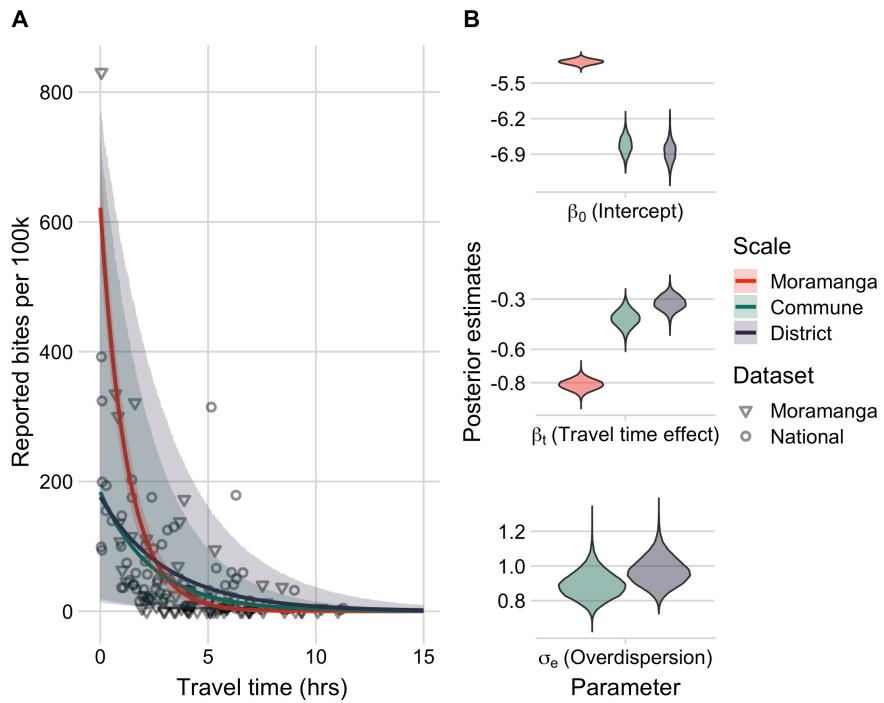
Deleted: a catchment random effect improved predictions (Fig S3.2 & Fig S3.3). However, after accounting for

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Deleted: were not clearly identifiable (Table S3.1) and the models resulted in similar predictions (Fig S3.6 & S3.7), indicating that catchment effects could not be differentiated from random variation in the data. Similarly, while the commune model fit to the Moramanga data generated stronger travel time effects (Fig 4B), after accounting for data overdispersion, the posterior estimates of the parameters overlapped for the commune and district models fit to the national data (Fig S3.4), and the model estimates were in general less robust to overdispersion than for the national data, particularly at low travel times (Fig S3.5). [Deleted: from](#)

554 travel time effects observed in our datasets. Moreover, our out-of-fit predictions to the
 555 data across scales suggest that the commune model is able to capture travel time
 556 impacts at the commune level (Fig S3.3), therefore we use both the district and
 557 commune model to disaggregate burden to the finest scale possible. Finally, we
 558 examined the sensitivity of models to how we corrected for underreporting of data, and
 559 found that parameter estimates of travel time impacts were similar across models and
 560 performed similarly in prediction (Fig S3.8 and Fig S3.9).

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561

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

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

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

577 In general, the incidence of rabies deaths increases with travel times to clinics, and
578 there is significant sub-national variation when deaths are modeled at the district and
579 commune scale, with the least accessible communities having most deaths (Fig 5B &
580 C). We estimate that under the current system of 31 clinics in Madagascar provisioning
581 PEP that approximately 800 (95% PI: 600 - 1000) deaths due to rabies are prevented
582 through PEP each year. Overall, we estimate close to 1000 rabies deaths (95% PI: 800
583 - 1100) annually in Madagascar. Our estimates vary only slightly depending on the

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Overall, we estimate close to 1000 rabies

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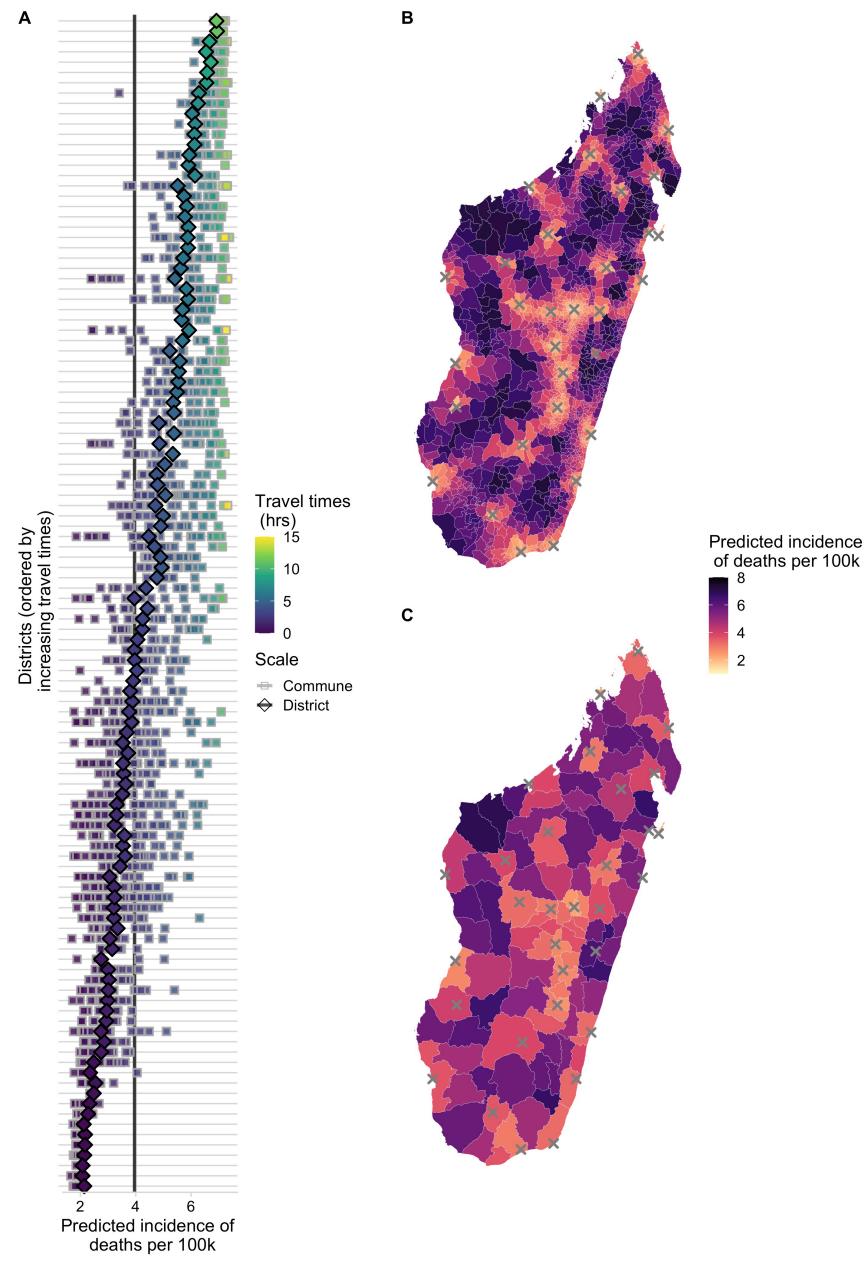
Deleted: Madagascar. Our estimates vary only slightly depending on the scale of the model (Table 2), but disaggregating deaths to the commune level shows considerable variation in predicted burden within districts (Fig 5A). Under the current system of 31 ARMCs in Madagascar, we estimate that use of PEP prevents approximately 800 (95% PI: 600 - 1000) deaths due to rabies each year.

596 scale of the model (Table 2), but disaggregating deaths to the commune level shows
597 considerable variation in predicted burden within districts (Fig 5A).

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

Model	Reported bite incidence per 100k	Burden of deaths	Deaths averted <u>by current PEP</u> <u>provisioning</u>
Commune	85 (56 - 129)	963 (795 - 1118)	801 (644 - 968)
District	85 (52 - 136)	958 (752 - 1156)	807 (609 - 1005)

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

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

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

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For a subset of additional clinics (n = 83, up to one
per district), we compared three methods of
ranking for expanding PEP provisioning.

614 We found that targeted expansion of PEP to clinics based on the proportion of the
615 population they reduced travel times for resulted in fewest deaths (Fig S5.1). Here we
616 report results from the commune model, as estimates were consistent across models
617 (Fig 6 and Supplementary appendix, section S5). We estimated that strategic PEP
618 expansion to these additional 83 clinics (1 per district) reduced rabies deaths by 19%
619 (95% PI: 14 - 23%) (Fig 6A). With one clinic per commune (where available, N = 1696),
620 we see a further reduction of 38% (95% PI: 30 - 46%). However, reductions in burden
621 saturate as more clinics are added (Fig S5.2). Even when all primary clinics provision
622 PEP, our model still predicts 600 (95% PI: 400 - 800) deaths per annum, and average
623 reporting of rabies exposures remains approximately 66% (95% PI: 33 - 78%) (Fig

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simulating expansion of PEP to a larger set of clinics (N
= 1733). ...

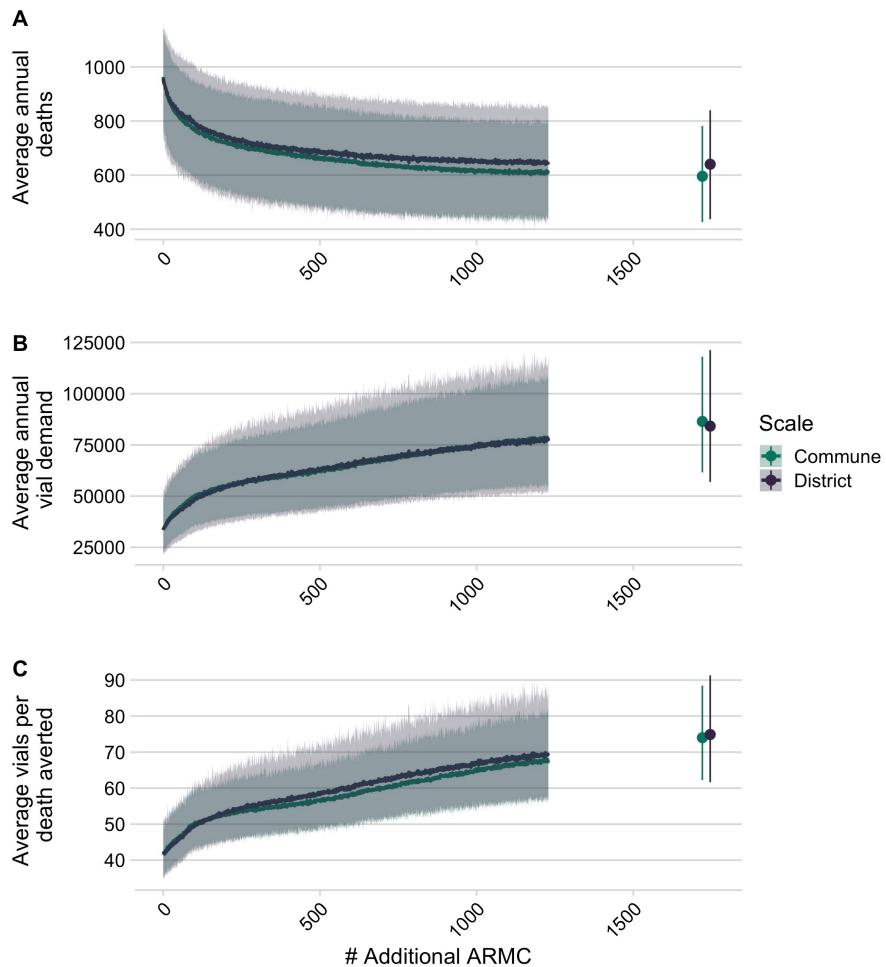
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634 S5.5); as more clinics are added, reported bite incidence saturates (Fig S5.4), and
635 patients shift which clinic they report to (S5.7 & S5.8).

636 Vial demand also outpaces reductions in burden (Fig 6B), with more vials needed per
637 death averted (Fig 6C). Our model predicts an increase from 33500 vials (95% PI:
638 22900 - 49400) per annum under current provisioning but with the abridged intradermal
639 regimen (i.e. visits on days 0, 3, 7), to ~56900 vials (95% PI: 40200 - 77800) with 250
640 clinics providing PEP, and ~86400 vials (95% PI: 61600 - 118000) if all primary clinics
641 provision PEP. In these scenarios, clinic catchment populations and throughput
642 decrease, with clinics seeing fewer patients per day (S5.6).

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644

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

647 (A) Decrease in deaths due to rabies, (B) increase in total # of vials as additional clinics Deleted: ARMC

648 provisioning PEP are added at the national level, and (C) increase in vials needed per Deleted:

651 death averted based on the two models of reported bites. Lines are the mean of 1000
652 simulations with envelopes representing 95% prediction intervals. The points show
653 when all additional primary clinics and secondary clinics ($N = 1733$) clinics have been
654 added).

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655 **Burden estimates are most sensitive to assumptions of underlying rabies
656 incidence.**

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To quantify which parameters contribute

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

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Deleted: estimates, we performed univariate

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Deleted:) and impacts of PEP access (Fig S6.2).

Deleted: Overall, while uncertainty in the underlying rabies exposure incidence results in considerable variation in our burden estimates, the projected impact of travel times and of access to PEP are qualitatively similar across parameter assumptions.

686 **Discussion**

687 **Main findings**

688 We find that the burden of rabies in Madagascar is likely concentrated in areas with
689 poor PEP access. We estimate that current PEP provisioning (at 31 clinics) averts
690 45% of deaths that would otherwise occur, and that expanding PEP access should
691 reduce mortality, with provisioning in one clinic per district ($N = 83$), or per commune (N
692 = 1733), expected to reduce mortality by 16% and 33%, respectively. However,
693 improved PEP provisioning is unlikely to eliminate rabies deaths; with over 600 deaths
694 expected even with PEP at all [primary clinics](#) ($N = 1733$). This is partly because travel
695 times remain high (> 2 hrs as estimated by the friction surface for over 10% of the
696 population, Fig S5.4) even after expanding PEP to all [primary clinics](#). With reduced
697 travel times, over 20% of exposures will still not seek PEP (Fig S5.5), resulting in ~1.65
698 rabies deaths per 100,000 people. PEP is expected to remain cost-effective as
699 provisioning expands, to a maximum of 450 USD per death averted (assuming 5 USD
700 per vial), similar to other estimates [4]. While our quantitative predictions depend on
701 assumptions of underlying rabies exposure incidence, the qualitative patterns regarding
702 travel time impacts remain robust and are useful in identifying strategies for provisioning
703 PEP.

704 **Limitations**

705 Data limitations introduced bias and uncertainty to our estimates. For example, travel
706 times from the [Malaria Atlas Project](#) friction surface underestimated patient-reported
707 travel times, with discrepancies between assigned transport speeds (from the Open

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714 Street Map user community, or country cluster data [18]) and realities of local travel. In
715 Madagascar, the presence of paved roads does not necessarily reflect their quality or
716 the modes of transport used. [Patients seeking PEP at the](#) Moramanga [clinic reported](#)
717 various transport methods and highly variable travel times even within a single
718 commune. While patient-reported travel times may lack precision from recall and
719 estimation error, they likely better reflect lived experience; validated travel times [30]
720 could improve estimates of spatial health inequities. Similarly, modeled estimates of
721 population distribution [19] also introduce uncertainty. Our analysis of data from the
722 Moramanga District [indicates](#) that variation at the sub-district level is high and impacts
723 health seeking behavior. However, we lacked fine-scale data from other catchments for
724 comparison. Additionally, we had to correct for underreporting and incomplete data;
725 strengthening surveillance and routine data collection should improve understanding of
726 health seeking behavior and access, and support monitoring and evaluation of PEP
727 provisioning.

728 [While we rely on a number of assumptions, they are based on data specific to](#)
729 [Madagascar or from other similar settings and consistent with estimates from the](#)
730 [literature more broadly \(see Table 1 and section S4\).](#) Our burden estimates were most
731 sensitive to assumptions about rabies exposure incidence, drawn from studies in the
732 Moramanga District [15] and elsewhere [4]. As incidence of rabies exposures varies
733 over time and space [31,32], we incorporated uncertainty into our estimates, but we did
734 not find qualitative differences in the effects of travel times on rabies deaths. Our
735 simplifying assumptions regarding patient compliance, which is generally high in
736 Madagascar [15], and on complete efficacy of PEP are unlikely to greatly influence our

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Deleted: We assumed geographic access to PEP was the primary driver of health-seeking behavior, but socioeconomic status, education and awareness about rabies [27,32–34] all play a role. In Madagascar, where PEP is free-of-charge, the main cost to patients is transport and time lost. More remote communities tend to be of lower socioeconomic and educational status [2], so travel time may be a proxy for these correlated variables. We also assume that all ARMC reliably provision PEP, but a 2019 KAP survey reported clinics experiencing stock-outs [25]. Most ARMC charge fees (from 0.50 - 3.00 USD for consultations, wound treatment, etc [25]) which may also act as barriers. Significant overdispersion in the data that cannot be explained by travel times suggests that clinic-level variation (e.g. vaccine availability and charges) and regional differences (e.g. dog populations, outbreaks, awareness) further influence health-seeking behavior and vaccine demand.¶

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762 burden estimates [22]. Likewise, we do not account for differential risk for severely
763 exposed patients not receiving Immunoglobulins (RIG), which is only available at IPM in
764 the capital of Antananarivo, but recent studies show that even in the absence of RIG,
765 PEP is extremely effective [4]. We also assume that clinics reliably provision PEP, but a
766 2019 KAP survey reported clinics experiencing stock-outs [25].

767 We assumed geographic access to PEP was the primary driver of health-seeking
768 behavior, but socioeconomic status, education and awareness about rabies [[33]; [27];
769 [34]; [35]; castillo2020behavioral] all play a role. For example, most PEP clinics also
770 charge fees (from 0.50 - 3.00 USD for consultations, wound treatment, etc. [25]) which
771 may also act as barriers to PEP access. In Madagascar, where PEP is free-of-charge,
772 the main cost to patients is transport and time lost. More remote communities tend to be
773 of lower socioeconomic and educational status [2], so travel time may be a proxy for
774 these correlated variables. Significant overdispersion in the data that cannot be
775 explained by travel times suggests that clinic-level variation (e.g. vaccine availability and
776 charges) and regional differences (e.g. dog populations, outbreaks, awareness) further
777 influence health-seeking behavior and vaccine demand. Although our estimates could
778 be improved with better data on rabies incidence, health-seeking behavior, and PEP
779 provisioning, predicting PEP impacts will remain challenging given the complex
780 interactions between socioeconomic factors, access to and quality of care, and human
781 behavior, as illustrated by the case studies in Box 1. However, it is very likely that the
782 impacts of improving access to PEP could be further increased with outreach and
783 awareness raising efforts that we were unable to parameterize.

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

787 1. Anosibe An'ala District (population ~ 100,265), south of Moramanga, has
788 moderate incidence of bite patients (~ 54/100,000 persons) even though travel
789 times often exceed 24 hours. While a road connects the main Anosibe An'ala
790 commune to the Moramanga PEP clinic, it is only passable by large trucks during
791 much of the rainy season, with speeds usually < 10km per hour. Over 9% of
792 patients from Anosibe An'ala had been in close proximity or touched a person
793 that died from rabies (four suspect human rabies deaths of patients who did not
794 receive any PEP), whilst of patients with Category II and III exposures that were
795 interviewed, 11/19 (58%) were bitten by probable rabid dogs. Given the high
796 travel times (although underestimated by the friction surface) and incidence of
797 reported rabies exposures and deaths, we predict a large but unobserved rabies
798 burden in this remote community (~6.02 deaths per year) and we ranked a clinic
799 provisioning PEP in Anosibe An'ala 28th for travel time reductions. Other remote
800 communities likely experience similar high and unrecognized burden, but
801 improved surveillance is necessary to identify such areas. Notably, bite patients
802 in this district demonstrate willingness to travel for free PEP (in some cases
803 walking 3 days to a clinic) with awareness of rabies risk. Community outreach
804 and active surveillance in other remote areas could also greatly improve people's
805 awareness of risk and health seeking behavior.

806 2. Recently, a middle-aged taxi driver died of rabies in suburban Antananarivo. The
807 day after being bitten by an unknown dog, he reported to a clinic that referred
808 him to the closest clinic provisioning PEP, approximately one hour's drive from
809 his home. His family urged him to go, but he did not believe his risk was high and
810 decided not to seek further care. He developed symptoms two weeks later and
811 was confirmed as a rabies death by the National Rabies Reference Laboratory.
812 Despite prompt reporting, appropriate referral, and socioeconomic indicators
813 suggesting a high care-seeking probability, this person did not receive PEP. His
814 story highlights the need for sensitization about rabies, how PEP provisioning at

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823 peripheral clinics (even in areas with reasonable access) could prevent additional
824 deaths, and ultimately that PEP alone is unlikely to prevent all rabies deaths.

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825 Broader context

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

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

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852 We predict that as clinics are expanded, throughput (daily patients reporting to a clinic)
853 will decrease. This may complicate the supply chain and make provisioning PEP more
854 challenging as vial demand becomes less predictable, leading to stock outs or wastage.

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855 Decentralized provisioning mechanisms, for example adopting routine childhood
856 vaccine supply chains, or novel vaccine delivery methods such as drones [48], may
857 mitigate these challenges. When nerve tissue vaccines were used in Madagascar,
858 clinics requested vaccines upon demand and PEP access was more widespread, but
859 provisioning the more expensive cell culture vaccines to all clinics became too costly
860 [16]. Widespread vaccine provisioning is therefore feasible given Madagascar's health
861 infrastructure, if cost barriers are removed.

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862 Gavi investment could greatly reduce the access and cost barriers to PEP [6,7,22,49].

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863 Currently, each clinic in Madagascar serves an average catchment of 780,000 persons.
864 Latin American countries, where significant progress has been made towards
865 elimination, aim for one PEP clinic per 100,000 persons. In Madagascar this would
866 require around 212 additional clinics provisioning PEP. We predict that Gavi investment
867 would be highly cost-effective, greatly reducing deaths by expanding PEP supply to
868 underserved areas.

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869 However, our results suggest that PEP expansion alone cannot prevent the majority of
870 rabies deaths, and even given maximal access, achieving 'the last mile,' preventing
871 deaths in the most remote populations, will require disproportionate resources [50]. To
872 achieve 'Zero by 30,' mass dog vaccination will be key to interrupting transmission and
873 eliminating deaths. Integrated Bite Case Management (IBCM) uses bite patient risk
874 assessments to determine rabies exposure status, guide PEP administration, and

880 trigger investigations of rabid animals, potentially identifying other exposed persons
881 [15,51,52]. IBCM is one way to manage PEP effectively [43] and as it relies on exposed
882 persons reporting to clinics, expanding PEP access could strengthen this surveillance
883 framework. These same issues of access, however, apply to both dog vaccination and
884 surveillance, and understanding spatial heterogeneities will be critical to determining
885 how control and prevention interventions can be best implemented [53,54].

886 **Conclusion**

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

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903 **Acknowledgements**

904 We thank all the clinicians and staff at the clinics across the country. We are grateful to
905 IPM and the Ministry of Public Health who collect and maintain data on PEP
906 provisioning. In particular, we thank the GIS unit for assistance with spatial data,
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908 Ratovoson, and Daouda Kassie for sharing results of their work in the Moramanga
909 District. In addition, we thank Jean Hyacinthe Randrianarisoa, Ranaivoarimanana,
910 Fierenantsoa Randriamahatana, Esther Noiarisaona, Cara Brook, Amy Winter, Christian
911 Ranaivoson, John Friar, and Amy Wesolowski for assistance.

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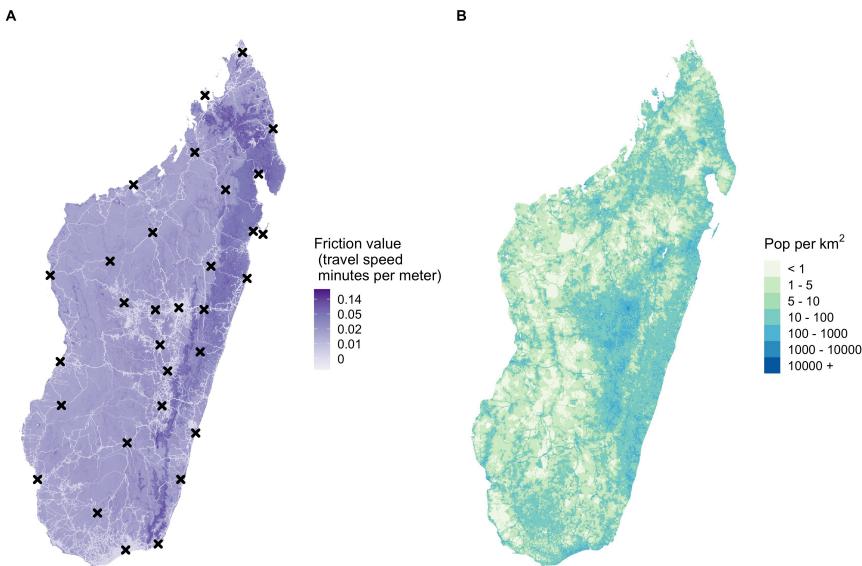
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1123 **Supplementary Appendix**

Commented [MR1]: A table of contents has been added to the clean version of the supplement.

1124 **S1. Estimating travel times to the closest clinic provisioning PEP**

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1126 **Fig S1.1. Raster inputs to estimate travel times to the closest clinic provisioning**

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1127 **PEP for Madagascar.**

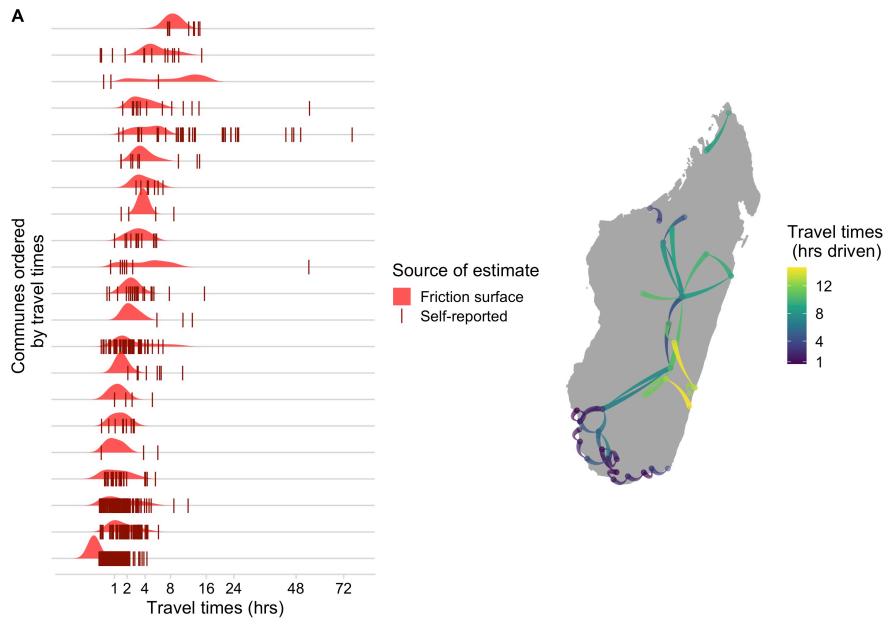
1128 **(A) Friction surface of travel speeds (in minutes per meter) at an $\sim 1 \times 1$ km scale, with**

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1129 **location of current clinics provisioning PEP (N = 31) shown with black x's. (B) Population**

1130 **estimates resampled to the same friction surface.**

1131



1135

1136 **Fig S1.2. Raw patient reported and driving travel time data.**

1137 (A) Distribution of travel times estimated at the grid cell level and reported by patients

1138 for each commune where patient data were available from the Moramanga PEP clinic

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1139 (B) Reported driving times between locations, with the color corresponding to the total

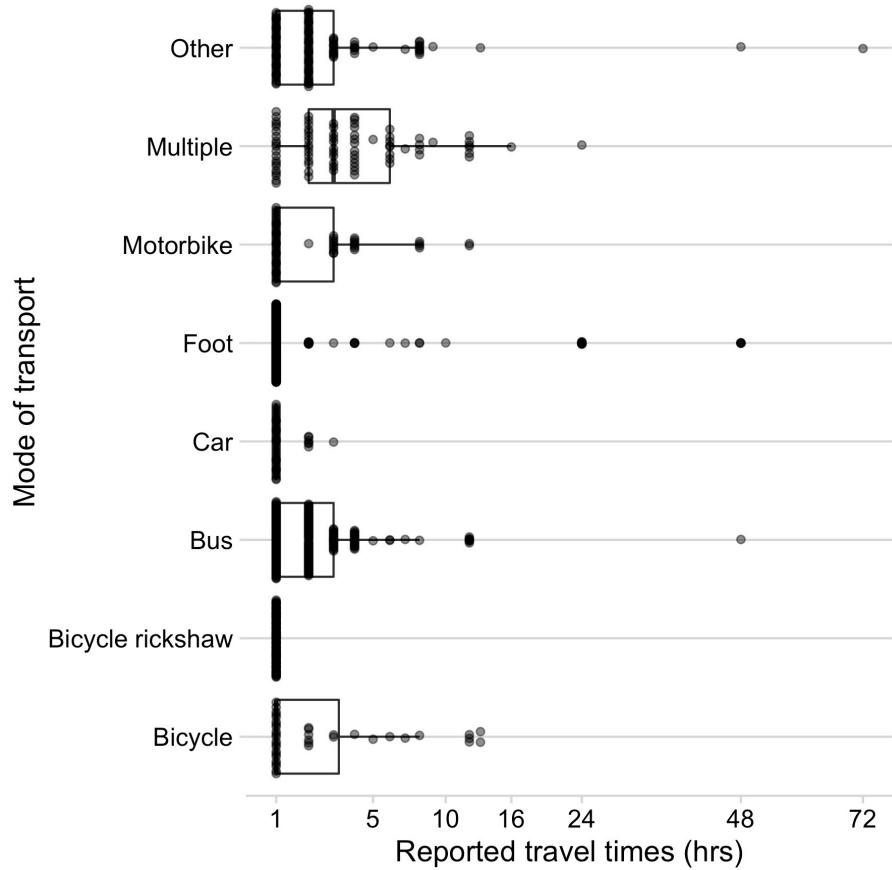
1140 driving time and the size of the line showing the direction of travel (narrow to wide ~

1141 origin to destination). Paths are Bezier curves from origin to destination, and do not

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1142 show actual paths driven.

1143

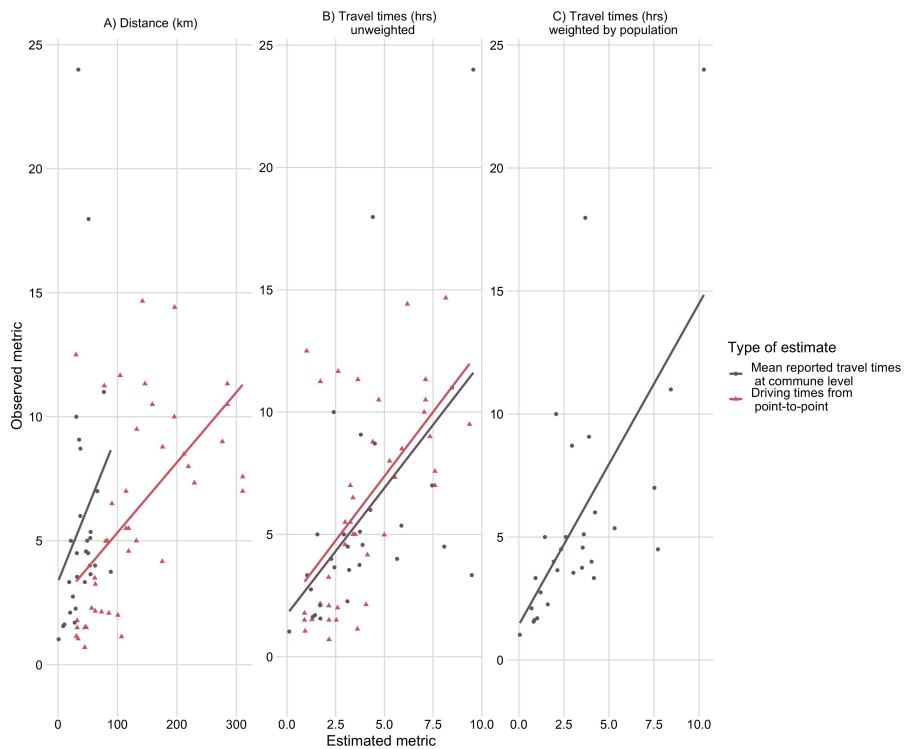


1146

1147 **Fig S1.3. Reported modes of transport used compared to reported travel times for**
 1148 **patients reporting to the Moramanga PEP clinic**

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1151

1152 **Fig S1.4. Observed estimates of travel times (commune means of patient reported**1153 **travel times and driving times between point locations) vs. estimates from friction**1154 **surface.**

1155 Predicted by (A) Distance (km) (Euclidean distance between origin and destination for

1156 driving times and distance from the commune centroid to the Moramanga **PEP clinic** for

1157 commune means) (B) Travel time estimates and (C) Travel time estimates weighted by

1158 population (for commune means only).

1159

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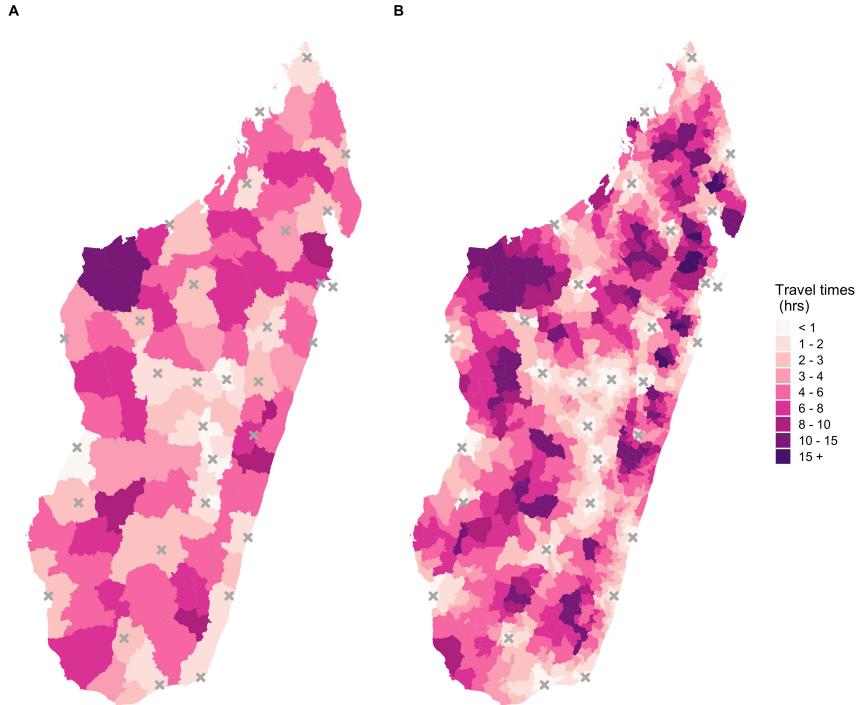
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1163 **Table S1.1.** *R*² values from linear models with estimated access metrics predicting
1164 either driving times or commune means of patient reported travel times.

Predictor	Driving times	Commune mean of patient reported travel times
Weighted travel times (hrs)	NA	0.433
Unweighted travel times (hrs)	0.347	0.290
Distance (km)	0.368	0.093

1165



1166

1167 **Fig S1.5. Estimates of mean travel times weighted by population at the (A) District**

1168 **(B) Commune scale.**

1169

1170 **S2. Estimating bite incidence**

1171 Most patients from each district reported to their closest clinic provisioning PEP by the
1172 weighted travel time metric (Fig 3). Accordingly, we assigned catchments based on
1173 which clinic was the closest for the majority of the population. While there are
1174 discrepancies between commune and district catchment assignments (Fig S2.1A), over
1175 75% of the population in a given district or commune were closest to a single clinic (Fig
1176 S2.1C). We excluded any clinics which submitted less than 10 forms (excluded 11
1177 catchments, Fig 3A grey polygons) and corrected for periods where clinics did not
1178 submit any forms.

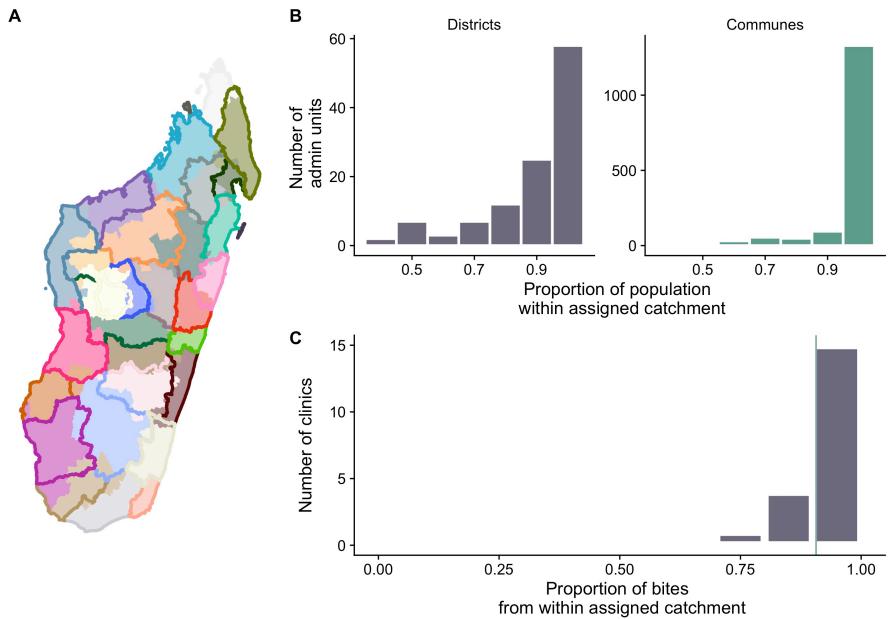
1179 Vial demand was simulated under simplified assumptions of PEP administration and
1180 adherence [15], based on patients reported randomly across the year. During this
1181 period, the Thai Red Cross Intradermal regimen was used across Madagascar, with 0.2
1182 mL administered per patient completing doses on days 0, 3, 7, and 28. Vials can be
1183 shared within a day between two patients, resulting in 0.1ml wastage per vial shared,
1184 plus any additional wastage from unused doses discarded at the end of the day. We
1185 estimate vial estimates as the midpoint estimate if all patients complete 3 vs. 4 doses.
1186 As clinic submission of forms was highly variable from 2014-2017 (Fig S2.2A), we
1187 compared estimated demand to the total vials provisioned across this four year period
1188 comparing different thresholds for correcting for periods of no form submission (i.e.,
1189 designating periods of 1, 5, 10, 15, and 30 consecutive days with zero submitted
1190 records as missing, compared to no correction).

1191 Estimates of vial demand based on uncorrected bite patient numbers were generally
1192 lower than the number of vials provisioned for those clinics with substantial under-

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1193 submission of forms (Fig S2.2B). Correcting patient numbers for under-submission
1194 resulted in estimates of vial demand closer to the provisioned vials for most clinics (Fig
1195 S2.2C, Table S2.1).

1196



1197

1198 **Fig S2.1. Catchment assignments by travel time.**

1199 (A) Catchments as assigned by closest clinic for the majority of the population within a
 1200 commune (polygon fill) or within a district (polygon outline). Admin units where the fill
 1201 and border colors do not match show places where assigned catchments differ at the
 1202 district vs commune scale. (B) Distribution of the proportion of the population in a given
 1203 administrative unit (district or commune) served by the catchment assigned. (C) The
 1204 proportion of bites reported to each clinic which originated from a district within the
 1205 assigned catchment. The vertical line indicates the proportion of bites from within the
 1206 assigned catchment for the Moramanga data (~90%).

1207

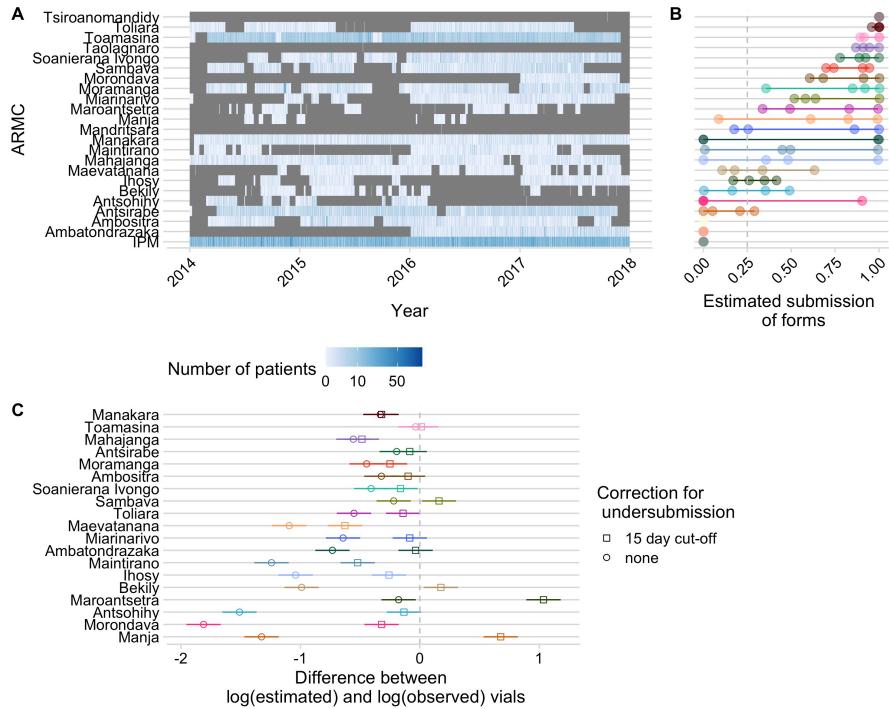


Fig S2.2. Estimating undersubmission of patient forms.

(A) Number of patient forms submitted to IPM for each clinic over the study period for each clinic, with periods of time where no forms were submitted for ≥ 15 days excluded (in grey); (B) Estimates for the proportion of forms submitted for each clinic (points are the estimate for each year and the line is the range), calculated as the # of days in a year which were not excluded based on the criteria of 15 consecutive days of non-submission/365. (C) The difference between log(estimated) and log(observed) vials provisioned for the period of 2013 - 2017 for each clinic correcting for under-submission

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1223 (squares) using the 15 day cut-off show in A and B, vs. not correcting for under-
1224 submission (circles). We did not have data on vials provisioned for IPM.

1225 **Table S2.1. Root mean squared error (MSE) between observed vials provisioned**
1226 **and estimated by the different consecutive day threshold for correcting for**
1227 **periods of no form submission, with the minimum root MSE in bold.**

Consecutive day threshold Root MSE

1	2346 38	Deleted: 37517191271
5	1038 45	Deleted: 44934372057
10	1015 88	Deleted: 87959359572
15	100682	Deleted: 81658615554
30	1063 39	Deleted: 38849847279
No correction	1658 48	Deleted: 47789086068

1228

1235 **S3. Modeling reported bite incidence**

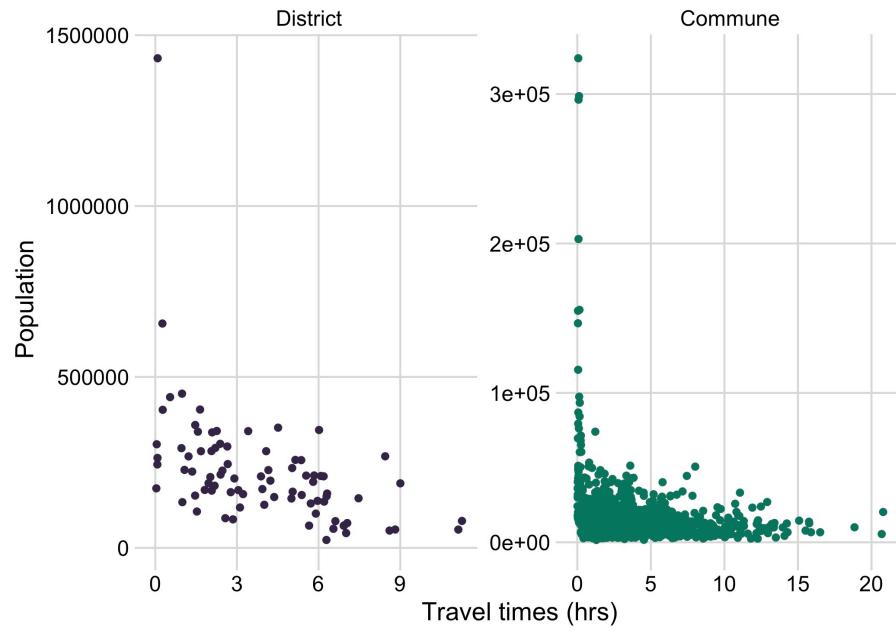
1236 We used a weakly informative prior for the intercept of the models centered around the
1237 mean of the bite incidence for the given dataset with a standard deviation of 10. For the
1238 covariate terms, we centered the priors around zero with a standard deviation of 10. For
1239 the variance terms (σ_0 and σ_e), we set uniform priors ($unif(0,5)$). We calculated the
1240 Deviance Information Criterion (DIC, a metric of model fit to data) for each candidate
1241 model as well as the maximum potential scale reduction factors (psrf) for each covariate
1242 and the multivariate psrf for the whole model (both are metrics of model convergence,
1243 where values < 1.1 are indicative of convergence, Table S3.1) [20].

1244 To test how well our models predicted the data, we sampled parameter estimates from
1245 the posterior distribution for each model to generate predictions to compare to data. In
1246 addition, we used the models to predict out-of-fit data (i.e. estimates from models fitted
1247 to the national data were used to predict the Moramanga data, and estimates from
1248 models fitted to the Moramanga data were used to predict the national data). Finally, to
1249 check how correcting for incomplete submission of forms affected our modeling results,
1250 we fitted our final models to the raw data uncorrected for submission (i.e. assuming
1251 forms were completely reported resulting in lower estimates of bite incidence) and with
1252 a lower cut-off (7 days, resulting in higher estimates of under-submission of forms).

1253 For the national data, including a catchment random effect improved predictions (Fig
1254 S3.2 & Fig S3.3). However, after accounting for overdispersion, catchment effects were
1255 not clearly identifiable (Table S3.1) and the models resulted in similar predictions (Fig
1256 S3.6 & S3.7), indicating that catchment effects could not be differentiated from random

1257 variation in the data. Similarly, while the commune model fit to the Moramanga data
1258 generated stronger travel time effects (Fig 4B), after accounting for data overdispersion,
1259 the posterior estimates of the parameters overlapped for the commune and district
1260 models fit to the national data (Fig S3.4), and the model estimates were in general less
1261 robust to overdispersion than for the national data, particularly at low travel times (Fig
1262 S3.5). Population size alone was the poorest fit to the data as estimated by DIC (Table
1263 S3.1), and models with population size as an additional covariate did not generate
1264 realistic predictions to the observed data or when used to predict out of fit (Figs S3.2
1265 and S3.3).

1266



1267

1268 **Fig S3.1. Correlation between travel time in hours (the average weighted by the**
 1269 **population) and population size of administrative units at the district and**
 1270 **commune scale.**

1271

1272 **Table S3.1. DIC and convergence estimates (maximum potential scale reduction**

1273 **factor and multivariate psrf, values < 1.1 indicate convergence) for all models.**

1274 *For the column pop effect, addPop = models with population size as additional
1275 covariate, onlyPop = models with population as only covariate, flatPop = models with
1276 population as offset in model. For the intercept type: random = random intercept by
1277 catchment, fixed = a single fixed intercept was estimated). The Overdispersion column
1278 indicates whether an overdispersion parameter was estimated (yes) or not (no).*

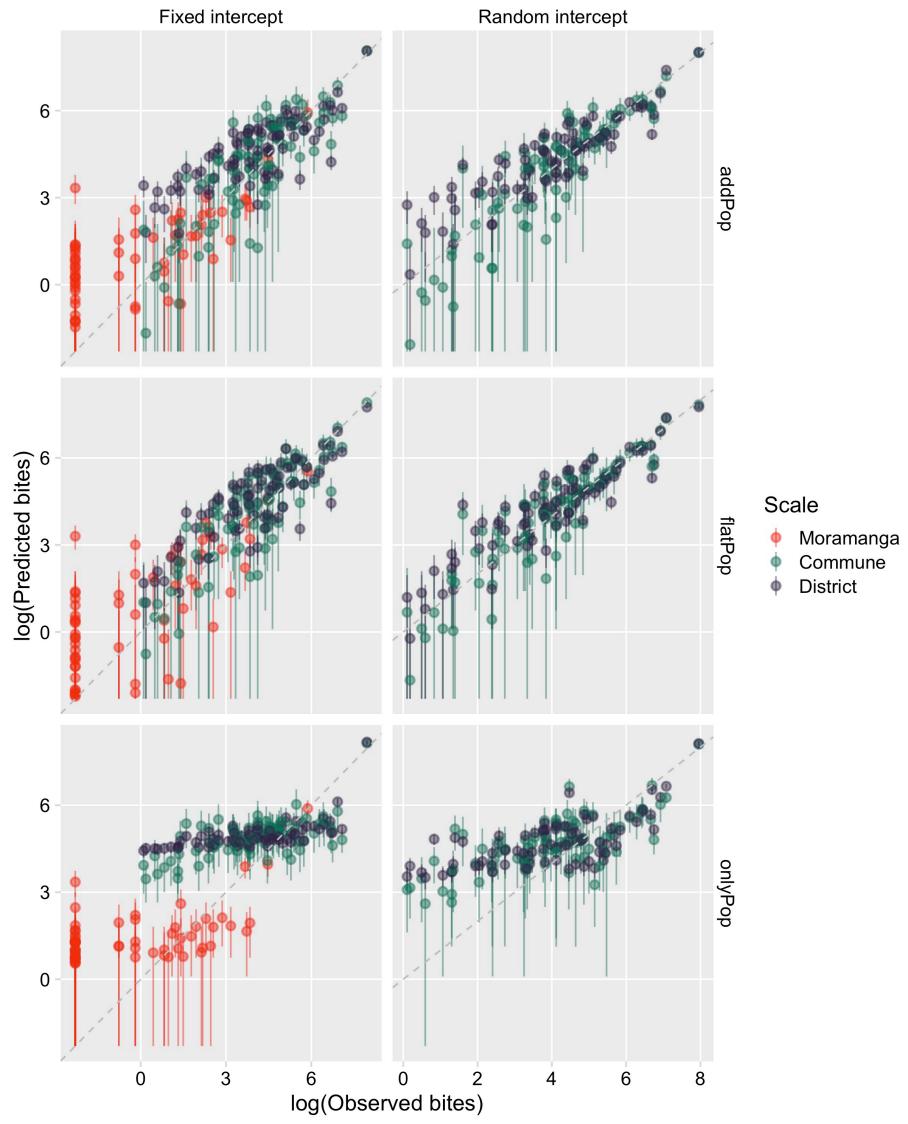
Dataset	Scale	Pop	Intercept		Overdispersion	DIC	Max	Multivariate
		effect	type	psrf				
Moramanga	Commune	flatPop	fixed	no		10.664	1.001	1
Moramanga	Commune	onlyPop	fixed	no		12.122	1.001	1
Moramanga	Commune	flatPop	fixed	yes		2.721	1.062	1.017
Moramanga	Commune	addPop	fixed	no		8.425	1.011	1.003
National	Commune	addPop	fixed	no		119.917	1.002	1.001
National	Commune	onlyPop	random	no		144.383	1.001	1.001
National	Commune	onlyPop	fixed	no		213.415	1	1

National	Commune	flatPop	random	no	41.936	1.001	1.001
National	Commune	addPop	random	no	50.287	1.001	1.001
National	Commune	flatPop	fixed	yes	6.784	1.028	1.008
National	Commune	flatPop	random	yes	6.793	1.393	1.102
National	Commune	flatPop	fixed	no	89.813	1.001	1
National	District	flatPop	fixed	no	113.715	1.001	1
National	District	addPop	fixed	no	124.957	1.001	1
National	District	onlyPop	random	no	126.176	1.002	1.001
National	District	onlyPop	fixed	no	189.105	1.001	1
National	District	flatPop	random	no	59.12	1.001	1.001
National	District	flatPop	fixed	yes	6.781	1.324	1.087

National District flatPop random yes 6.783 1.122 1.069

National District addPop random no 61.133 1.004 1.001

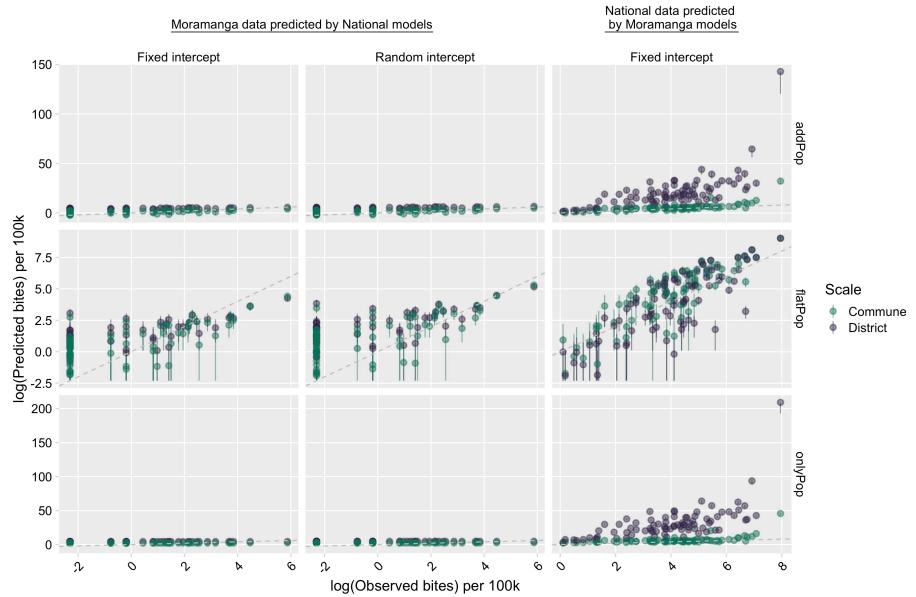
1279



1281 **Fig S3.2. Prediction to data used to fit each model.**

1282 Log of the observed bites against the log of predicted bites generated from sampling
1283 1000 independent draws from the posterior distributions for each parameter, with the
1284 points the mean of the predictions and the linerange the 95% prediction intervals.
1285 Columns are by the type of model intercept (either a fixed intercept or a random
1286 intercept by catchment) and rows are the type of model structure with respect to the
1287 population covariate (addPop = population size as additional covariate, onlyPop =
1288 population as only covariate, flatPop = population as offset in model). Colors show
1289 which data set was used for fitting and the scale of the model (Moramanga =
1290 Moramanga data with covariates at the commune level, Commune = National data with
1291 covariates at the commune level, District = National data with covariates at the district
1292 level).

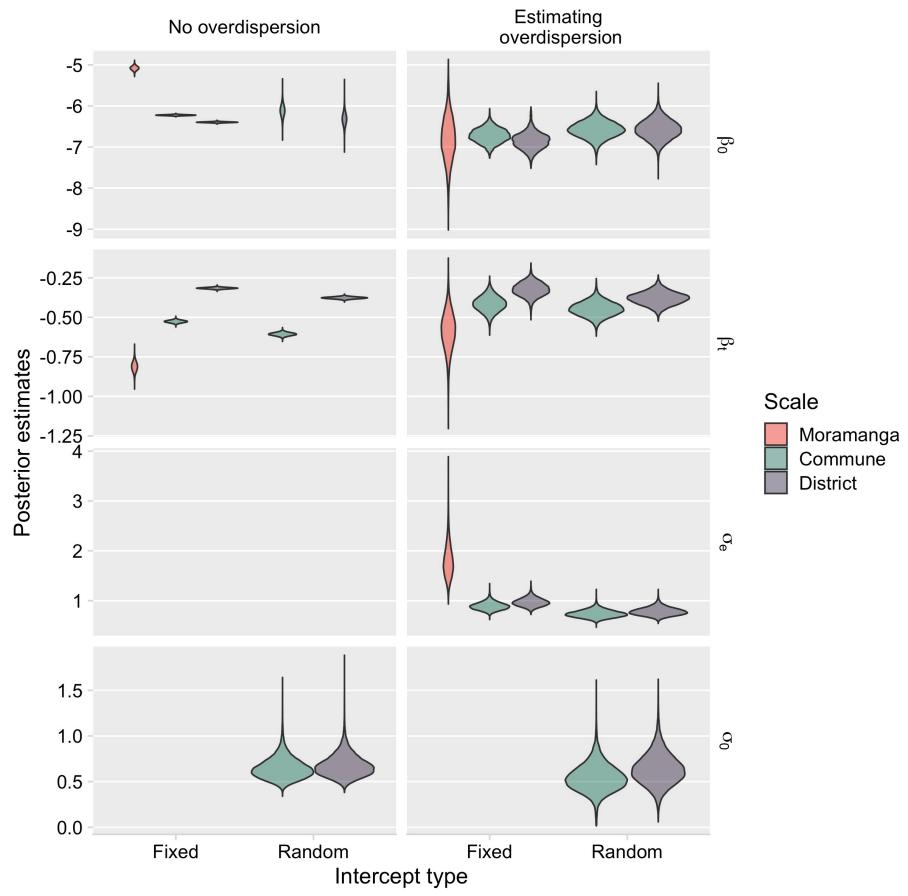
1293



1294

1295 **Fig S3.3. Out of fit predictions to data.**

1296 Log of the observed bites against the log of predicted bites for data not used to fit the
 1297 model. Predictions were generated by sampling 1000 independent draws from the
 1298 posterior distributions for each parameter, with the points the mean of the predictions
 1299 and the linerange the 95% prediction intervals. The first two columns are the predictions
 1300 from the commune and district model fitted to the national data for the Moramanga data
 1301 with fixed and random intercepts. The third column are predictions from models fitted to
 1302 the Moramanga data for the national data at the commune and district scale (only fixed
 1303 intercept models). Rows are the type of model structure with respect to the population
 1304 covariate and colors show which data set was used for fitting as per Fig S3.2.



1305

1306 **Fig S3.4. Posterior estimates of parameters from models with travel time and**

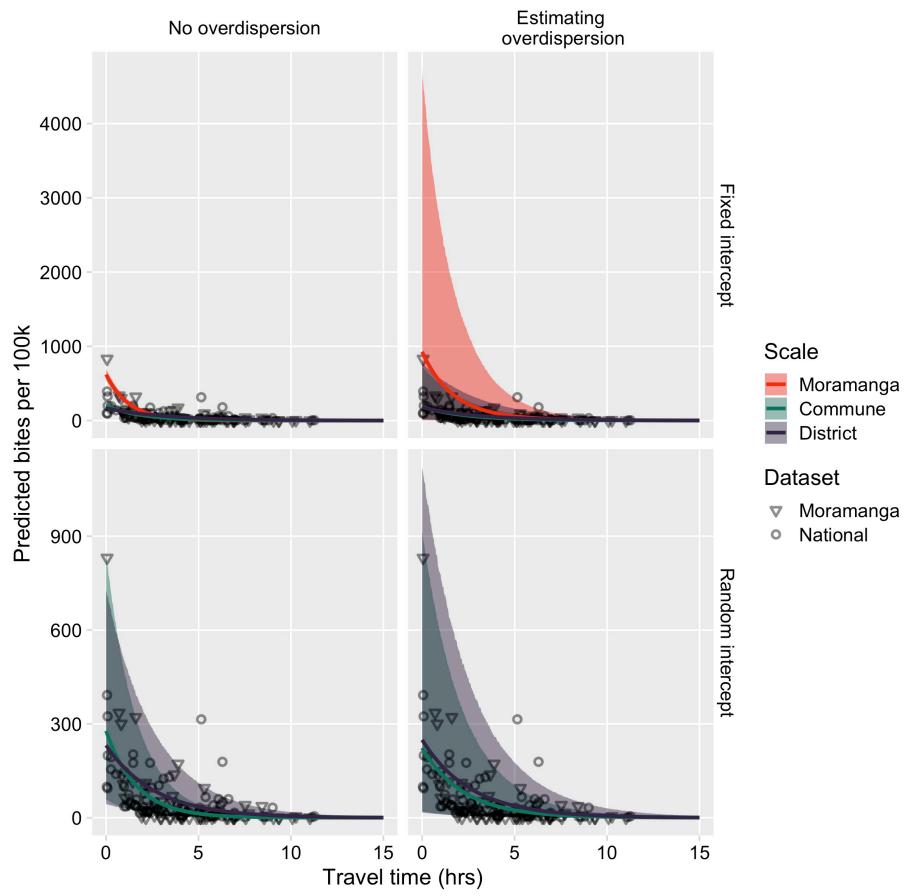
1307 **population as an offset.**

1308 Comparing models accounting for overdispersion (σ_e) compared to models with no

1309 overdispersion parameter (flatPop in Figs S3.2 & S3.3). For the Moramanga model, as

1310 data came from a single catchment, models with a random catchment effect (σ_0) were
1311 not fitted.

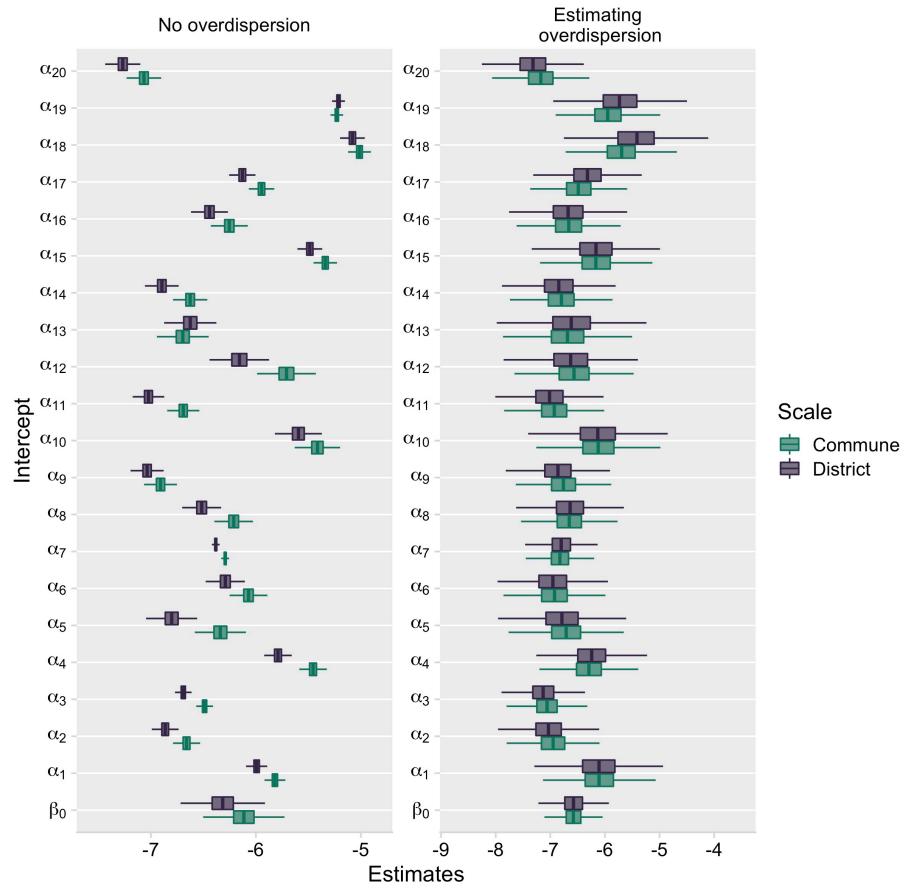
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1313

1314 ***Fig S3.5. Predicted relationship between travel times (in hours) and reported bite***
1315 ***incidence per 100,000 persons.***

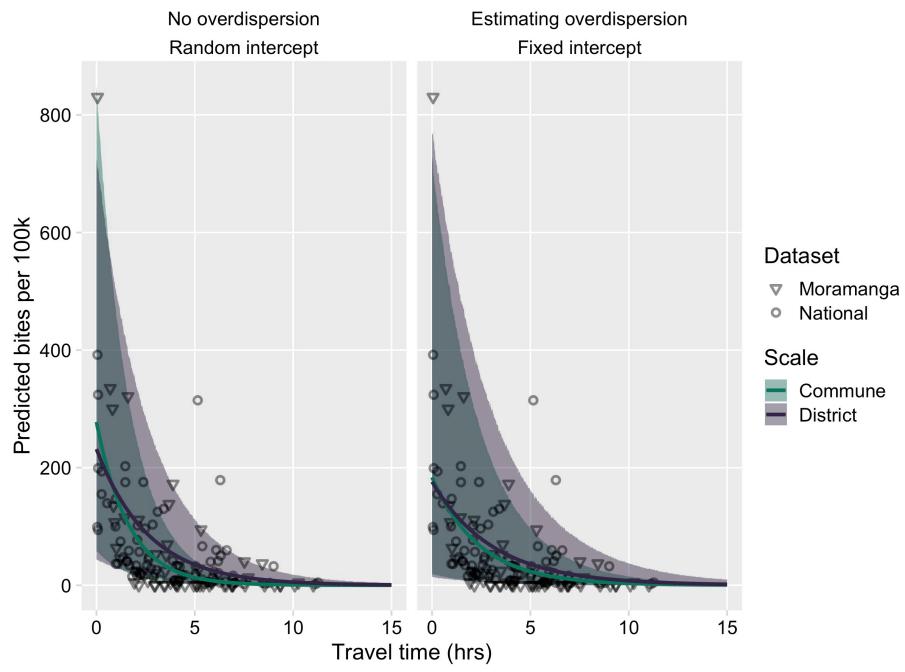
1316 *Generated from sampling 1000 independent draws from the posterior distributions for*
1317 *each parameter, with the line the mean of the predictions and the envelopes showing*
1318 *the 95% prediction intervals. Rows are by the type of model intercept (either a fixed*
1319 *intercept or a random intercept by catchment) and columns are whether the model*
1320 *estimated an overdispersion parameter. The points show the data used to fit the models*
1321 *(the National dataset), as well as the Moramanga dataset. Note the different y-axis*
1322 *limits between the fixed and random intercept models.*



1323

1324 **Fig S3.6. Posterior estimates of the catchment intercepts (α parameters, with β_0**
 1325 **the estimated mean intercept) for models with and without an overdispersion**
 1326 **parameter.**

1327



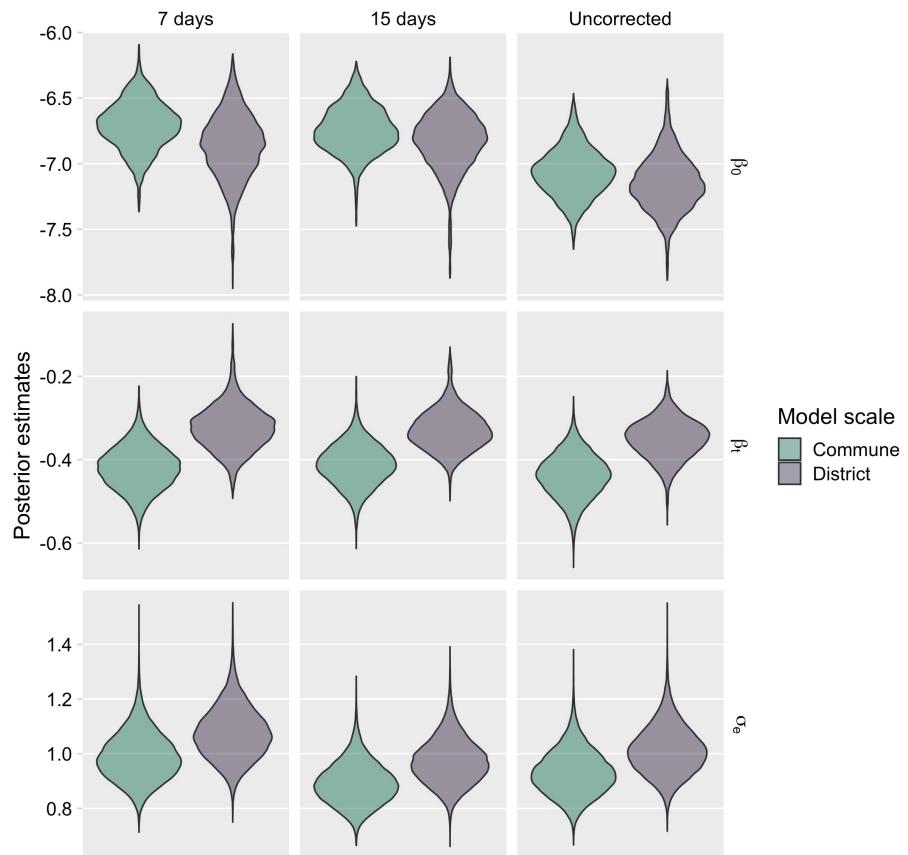
1328

1329 **Fig S3.7. Predicted relationship between travel times (in hours) and reported bite**

1330 **incidence per 100,000 persons.**

1331 *For random intercept model without overdispersion vs. fixed intercept model with
 1332 overdispersion, generated from sampling 1000 independent draws from the posterior
 1333 distributions for each parameter, with the line the mean of the predictions and the
 1334 envelopes showing the 95% prediction intervals. The points show the data used to fit
 1335 the models (the National dataset), as well as the Moramanga dataset.*

1336



1337

1338 **Fig S3.8. Posterior estimates for models with population as an offset and an**

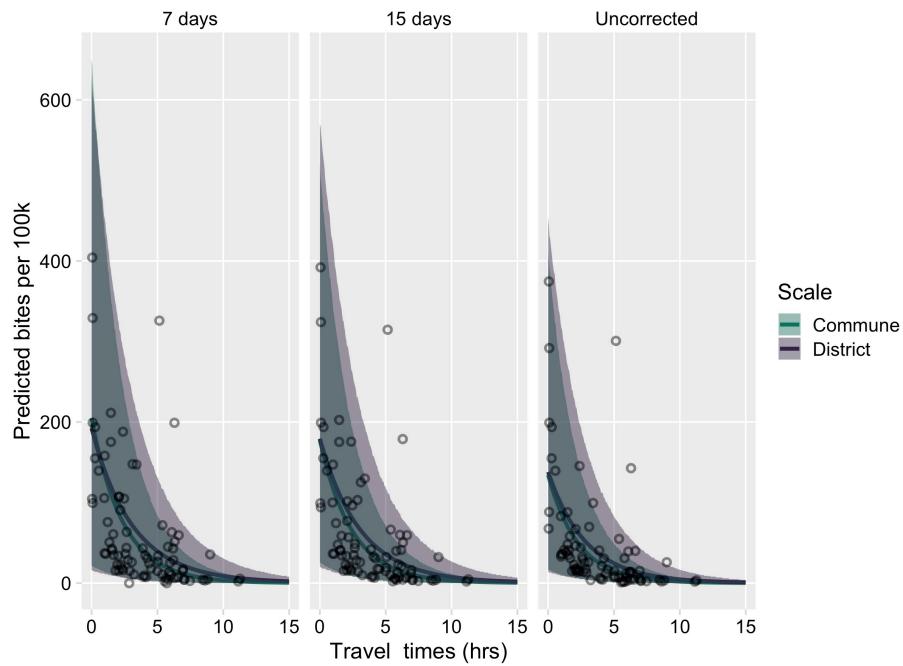
1339 **overdispersion parameter.**

1340 *Columns show estimates from models fitted to the national dataset (1) corrected for*

1341 *both under-submission by correcting for periods of at least 7 days where zero patient*

1342 forms were submitted, (2) correcting for periods of 15 days where zero patient forms
1343 were submitted, and (3) with the raw data not correcting for under-submission.

1344



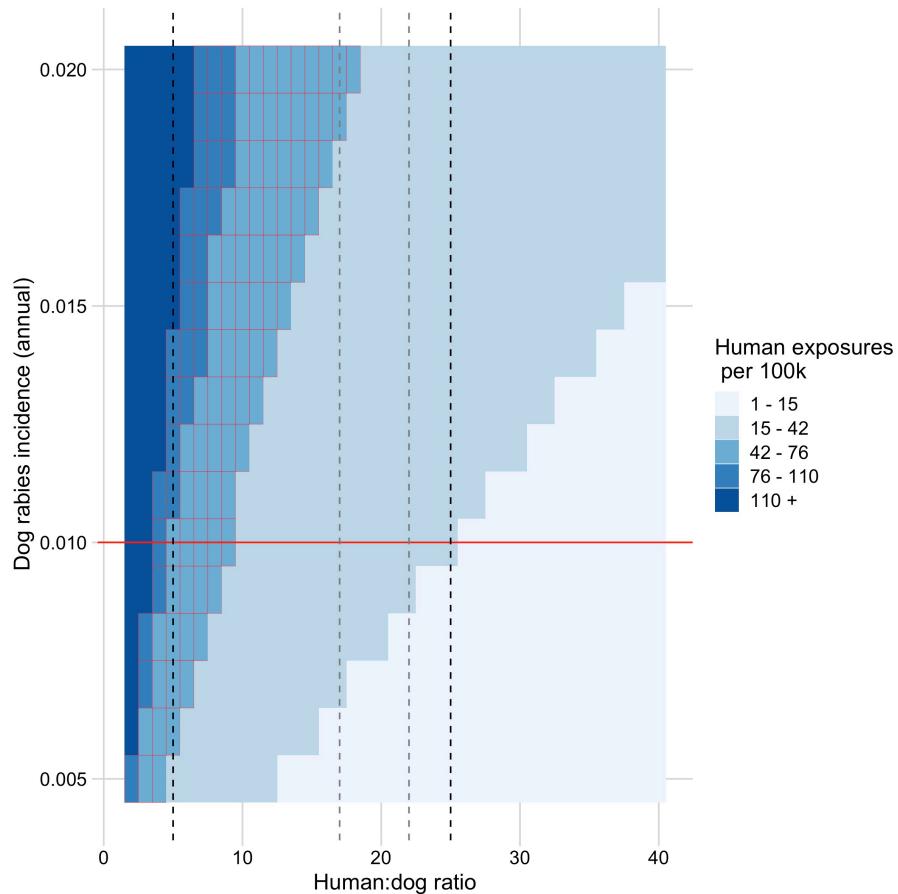
1345

1346 **Fig S3.9. The estimated relationship between travel time in hours (x-axis) and**
1347 **mean annual bite incidence per 100,000 persons (y-axis).**

1348 For models with population as an offset and an overdispersion parameter. Panels show
1349 predictions from models fitted to the national dataset 1) correcting for periods of at least
1350 7 days where zero patient forms were submitted (a less stringent cutoff resulting in
1351 lower estimates of the proportion of forms submitted and thus higher estimates of

1352 reported bite incidence), (2) correcting for periods of 15 days where zero patient forms
1353 where submitted, as presented in the main analysis, and (3) with the raw data not
1354 correcting for under-submission (resulting in lower estimates of reported bite incidence).
1355 Predictions were generated from sampling 1000 independent draws from the posterior
1356 distributions for each parameter, with the line the mean of the predictions and the
1357 envelopes showing the 95% prediction intervals. The points show the data used to fit
1358 the models.

1359 **S4. Range of rabies exposure incidence in people**



1360

1361 **Fig S4.1. Estimated exposures per 100,000 given a range of human to dog ratios**

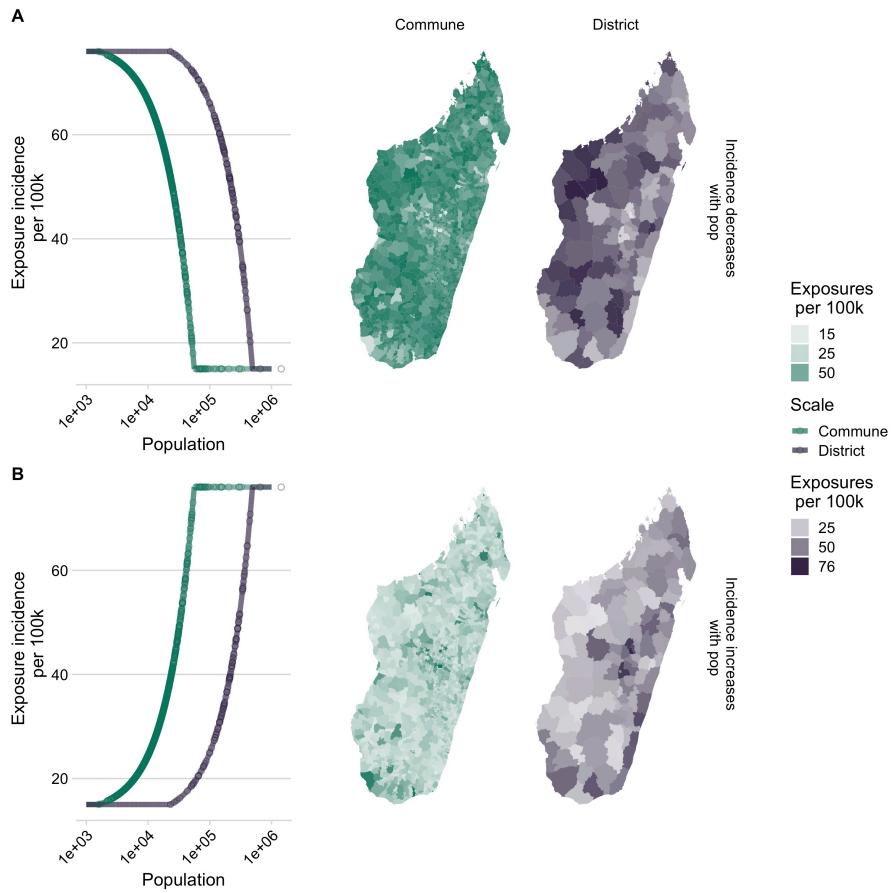
1362 **(HDRs, x-axis) and annual dog rabies incidence (y axis).**

1363 Assuming that each dog on average exposes 0.39 persons [55]. The black dashed lines

1364 show the range of human to dog ratios (HDRs) we use in the main analysis to estimate

1365 the range of human exposure incidence (where the red horizontal line and black dashed
1366 lines intersect). The grey dashed lines show the HDRs estimated from the Moramanga
1367 district from a recent study [24]. The cells with red outlines show the range of estimated
1368 exposure incidence from a previous study of bite patients in Moramanga District [15].

1369

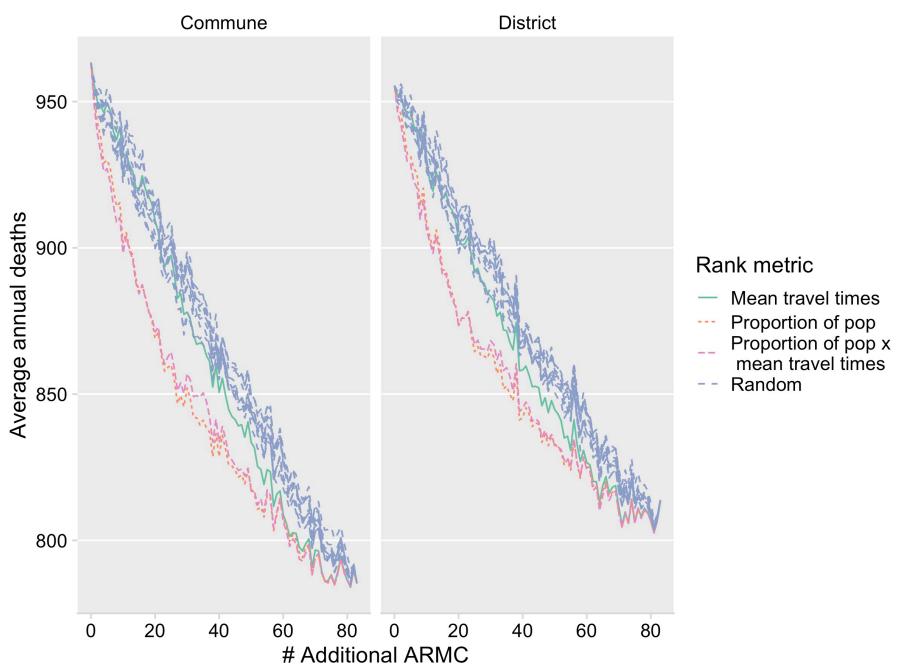


1371 **Fig S4.2. Range of constrained scaling factors generated for district and**

1372 **commune population size**

1373 *Underlying rabies exposures either (A) decreases with increasing population size or (B)*
1374 *increases with increasing population size across a fixed range of exposure incidence*
1375 *(15.6 - 76 exposures/100k persons). Lines show the expected relationship, with points*
1376 *showing where administrative units fall along this curve, and maps show how this*
1377 *results in variation in assumed exposure incidence spatially at the commune and district*
1378 *level.*

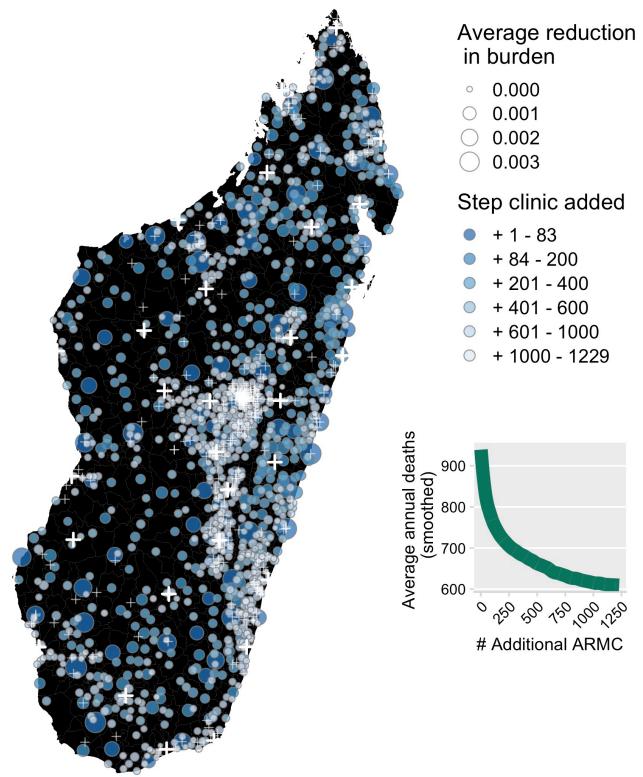
1379 **S5. Estimating the impact of expanding PEP provisioning to additional clinics**



1380

1381 **Fig S5.1. Comparing metrics for ranking clinics for targeted expansion.**

1382 We simulated expansion using three different ranking metrics: 1) reduction in mean
1383 travel times (green line) 2) the proportion of the population for which travel times were
1384 reduced (red dashed line) and 3) the proportion of the population for which travel times
1385 were reduced weighted by the reduction in travel times (pink dashed line). For each of
1386 these, we simulated burden using our decision tree framework (y axis is the mean of
1387 1000 simulations of annual deaths at the national level). The blue lines show 10
1388 simulations of randomly expanding access on reducing burden as a comparator. The
1389 panels show to the commune and district model of reported bite incidence.



1390

1391 **Fig S5.2. Map of the location and at what step each clinic was added.**

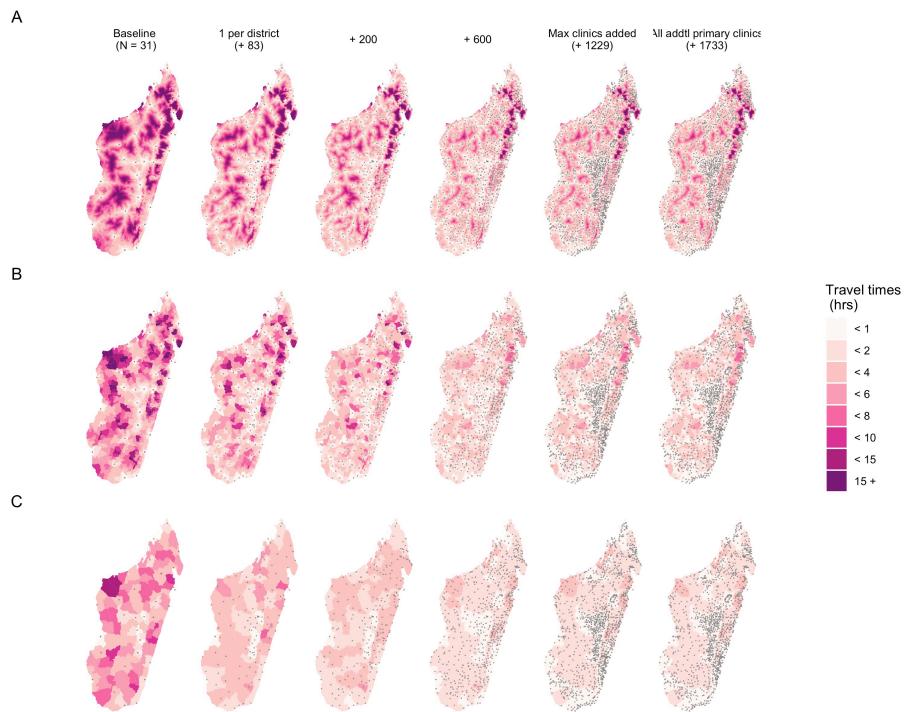
1392 The circles are each of the primary clinics across the country sized by the resulting
 1393 average reduction in burden (based on smoothed annual burden estimates from the
 1394 commune model, see inset). The large white crosses show the location of the existing
 1395 31 clinics provisioning PEP in Madagascar and the smaller white crosses are the

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1398 additional primary clinics in the country which were added in the final step but not
1399 ranked.

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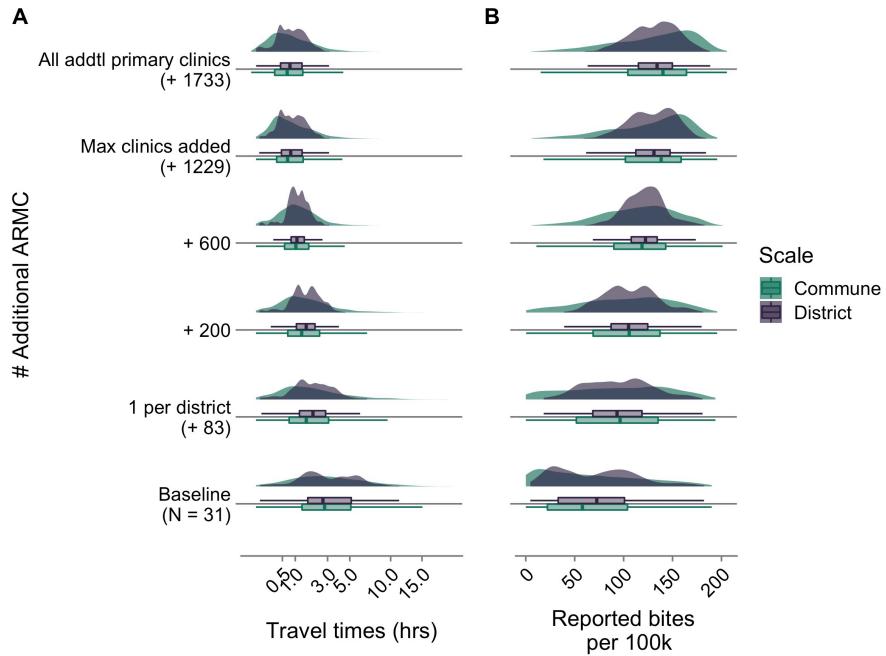
1400
1401 **Fig S5.3. Maps of how travel times change as clinics are added.**

1402 (A) at the ~1 x 1 km grid cell (B) commune and (C) district scales. The columns are
1403 ordered by the number of clinics at each step: baseline (N = 31), + 83 (1 per district), +
1404 200, + 600, + 1406 (1 per commune), and max (+ 1696 clinics, all additional primary
1405 clinics in the country). Grey pixels show the location of clinics provisioning PEP at each

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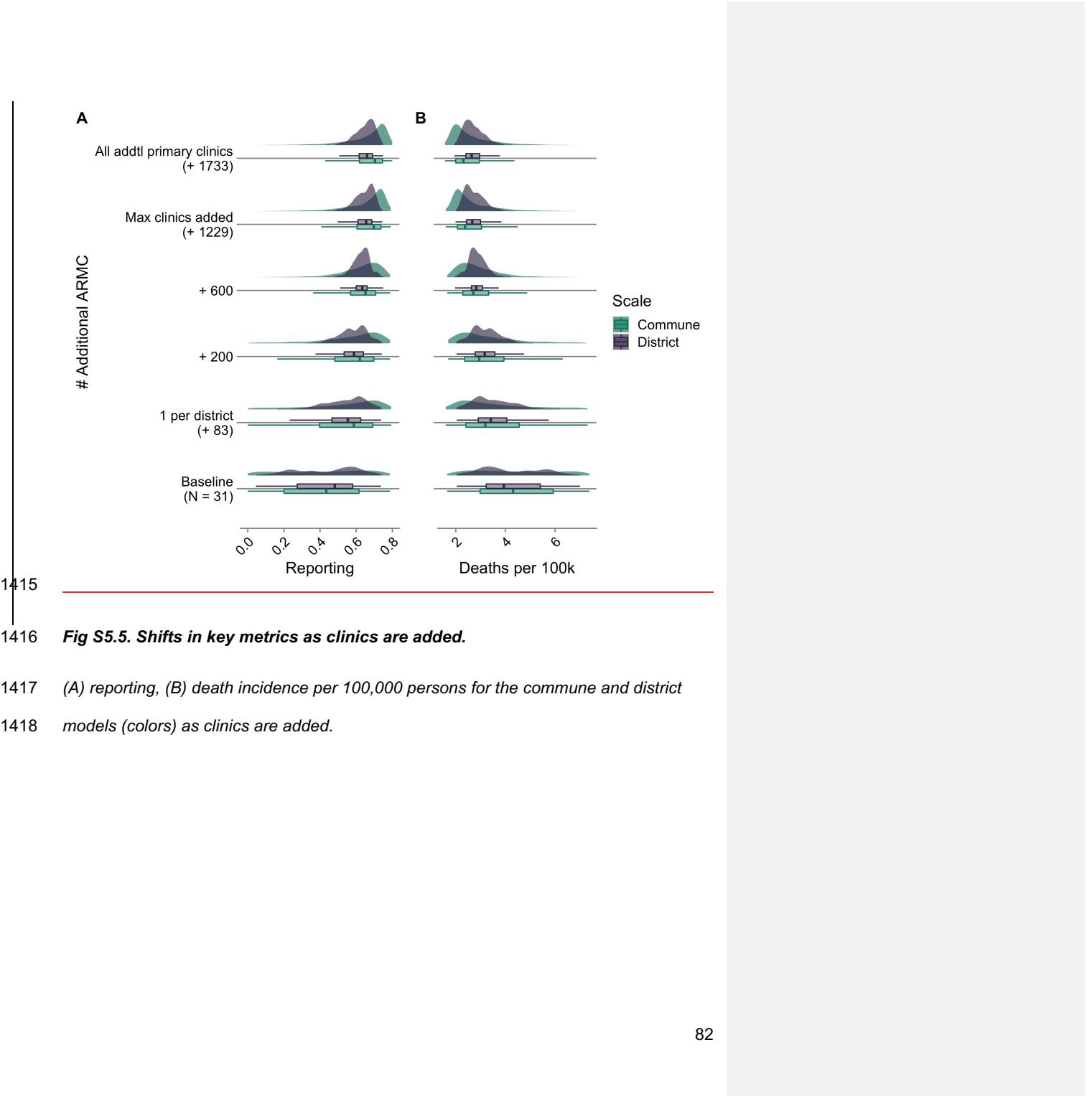
1409 step. Commune and district values are the average grid cell travel times weighted by
1410 the population in each cell.

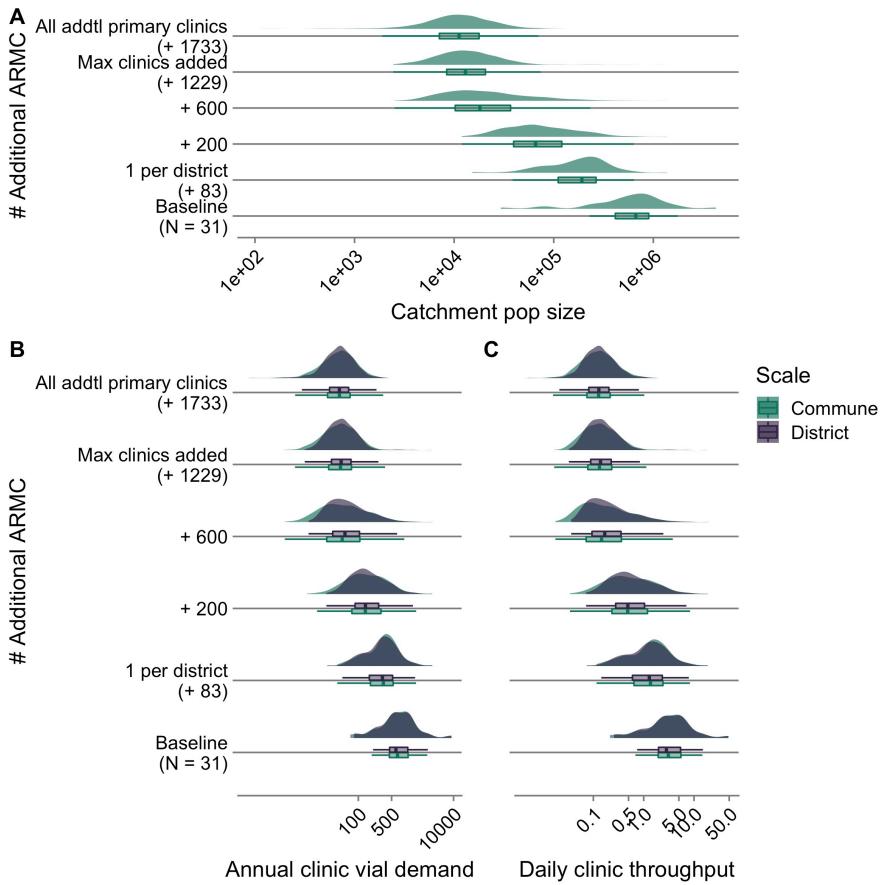


1411

1412 **Fig S5.4. Shifts in key metrics as clinics are added.**

1413 (A) travel times (hrs, x-axis is square root transformed), (B) bite incidence per 100,000
1414 persons and boxplots showing the median for communes and district models (colors).



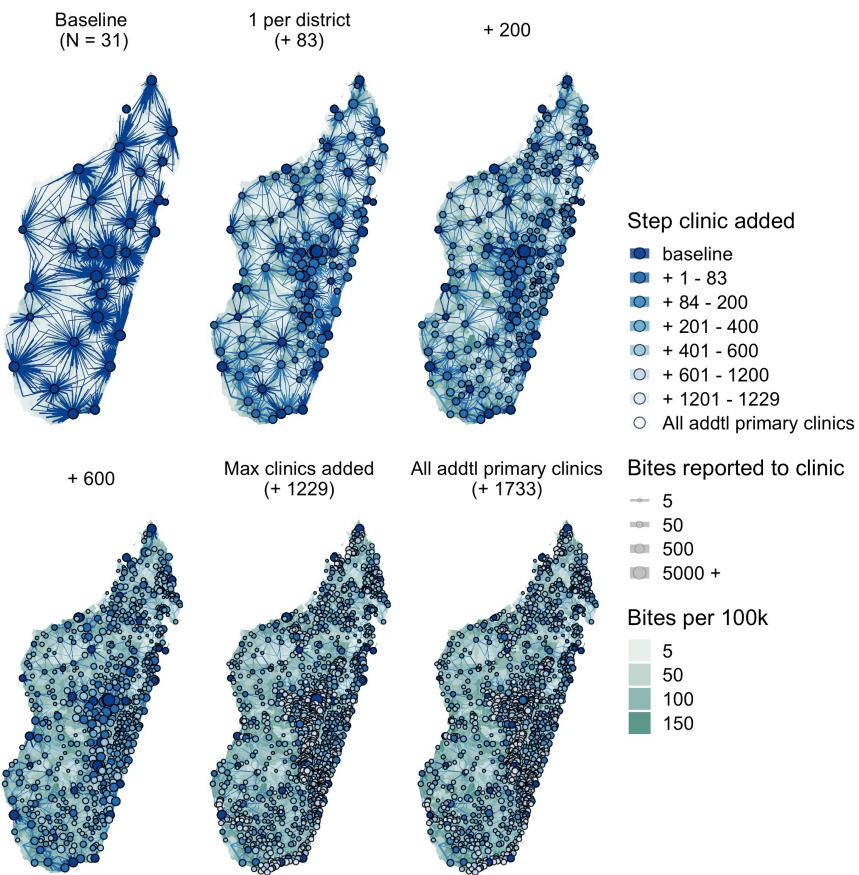


1419

1420 **Fig S5.6. Shifts in key metrics as clinics are added.**

1421 (A) catchment population size, (B) annual vial demand, and (C) daily throughput
 1422 (i.e. average number of patients reporting each day) given estimates of bite incidence
 1423 for the commune and district models (colors). For vial demand estimation, catchment
 1424 population sizes are the same for each model as these populations are allocated at the

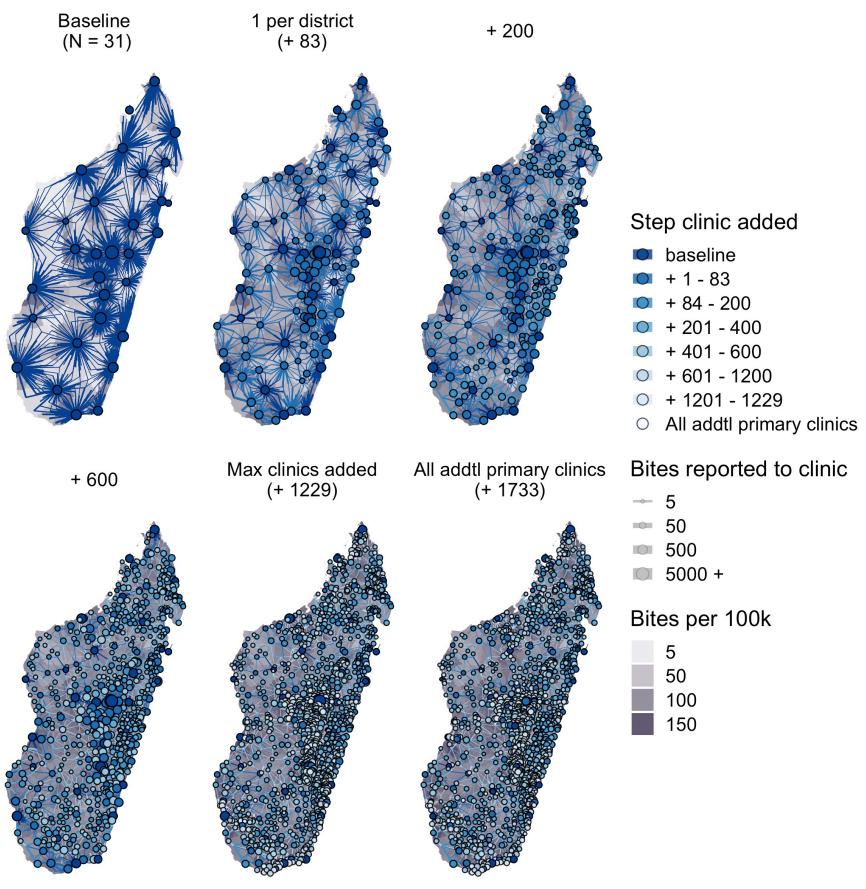
1425 grid cell level (i.e. population in a grid cell is allocated to the clinic catchment it is closest
1426 to in terms of travel times regardless of district or commune). All x-axes are log
1427 transformed.



1428

1429 ***Fig S5.7. Shifts in where bites are reported to as clinics are added for the***
1430 ***commune model.***

1431 *The circles show the clinic locations for each scenario, with size proportional to the*
1432 *annual average bites reported to that clinic. Lines show where the bites are reported*
1433 *from (commune centroid) also proportional to the number of bites. The polygon shading*
1434 *shows the commune level reported bite incidence.*



1435
1436 **Fig S5.8. Shifts in where bites are reported to as clinics are added for the district**

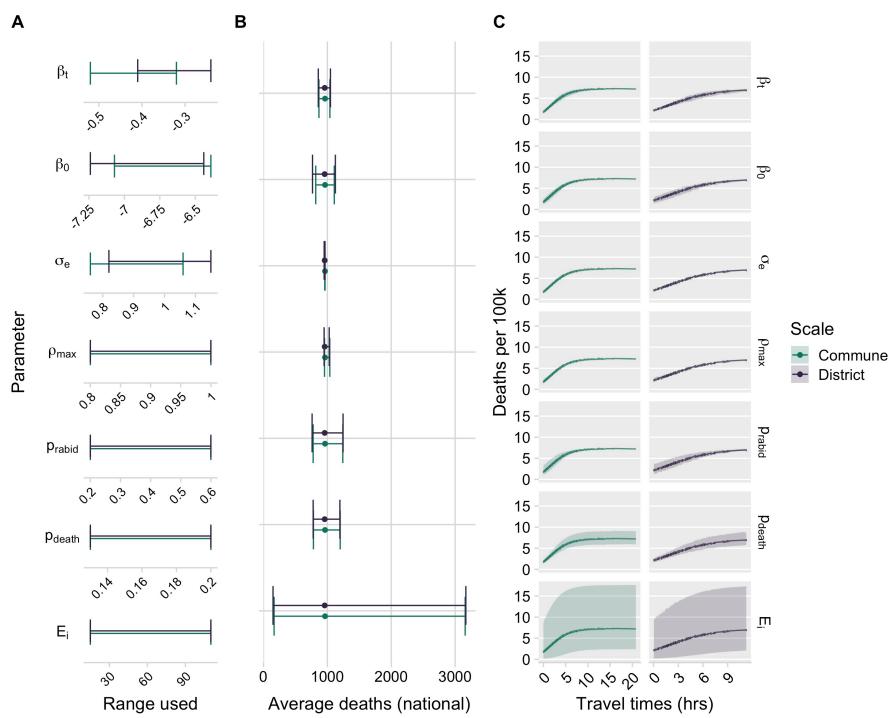
1437 **model.**

1438 The circles show the clinic locations for each scenario, with size proportional to the
1439 annual average bites reported to that clinic. Lines show where the bites are reported
1440 from (commune centroid) also proportional to the number of bites. The polygon shading

1441 shows the district level reported bite incidence.

1442

1443 S6. Sensitivity of burden estimates to parameter assumptions



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1444

1445 Fig S6.1. Sensitivity analyses for baseline burden estimates.

1446 (A) Range of parameters used in the univariate sensitivity analysis (upper 97.5% and

1447 lower 2.5% credible interval of posterior for the parameters in the bite incidence

1449 model, 95% of CI from 95% CI of estimate from [22] for ρ_{\max} , and fixed at the minimum

1450 and maximum of the range used in the main analysis for all other parameters) (B)

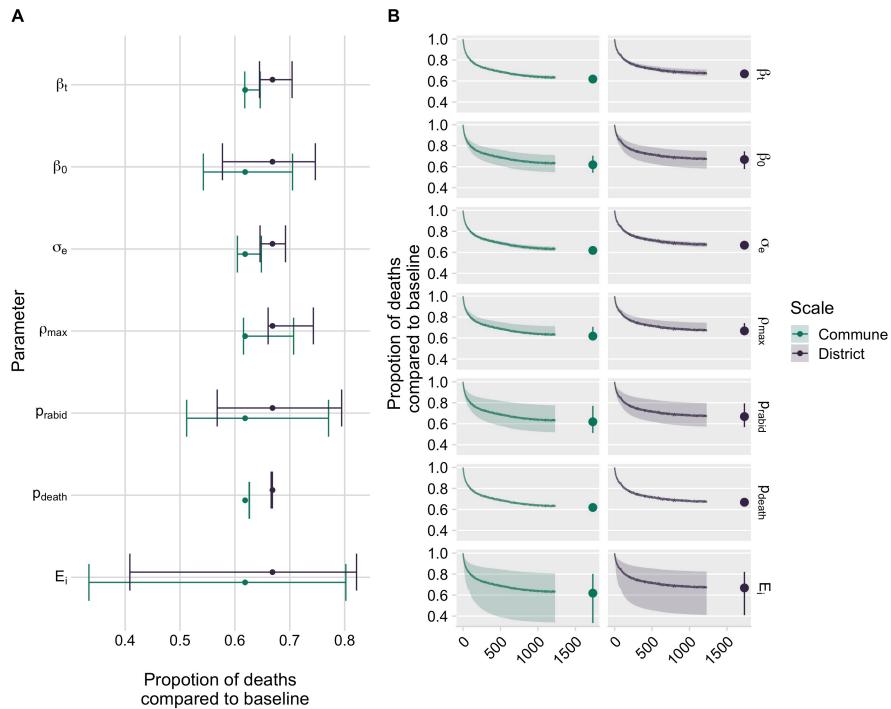
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1454 Range of estimates of the estimate average deaths at the national level for range of
1455 parameter estimates (point shows the estimate presented in the main analyses and the
1456 ends show the upper and lower estimates for the parameter range) and (C) estimates
1457 for the predicted relationship between travel times and incidence of human rabies
1458 deaths across the same parameter ranges (line shows the estimate presented in the
1459 main analyses and the envelope shows the upper and lower estimates for the
1460 parameter range) for the two models (colors). See Table S6.1 & 2 for ranges used for
1461 each parameter.

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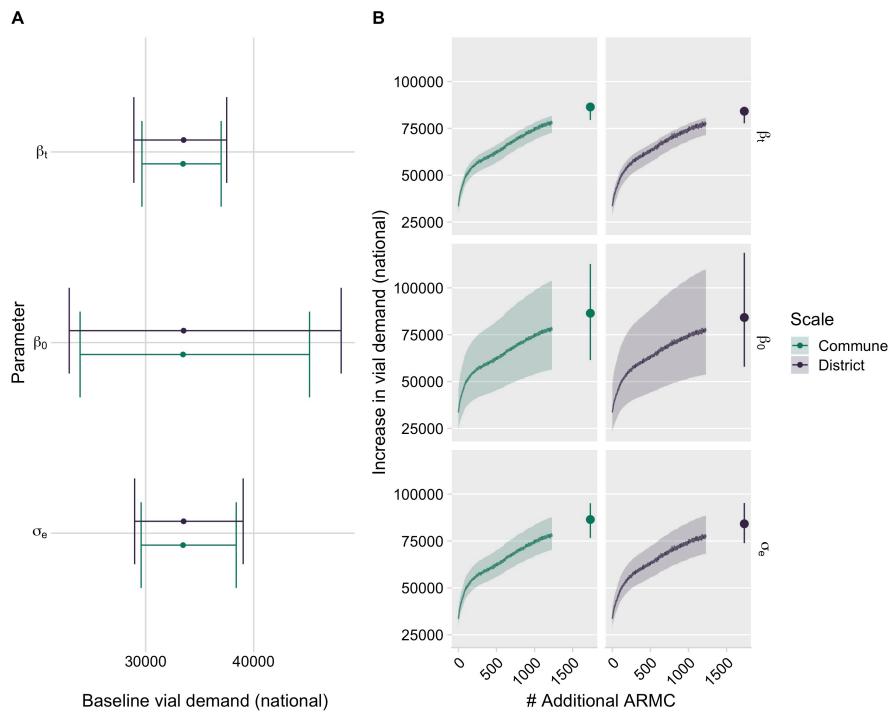
1465 **Fig S6.2. Sensitivity analysis for PEP expansion.**

1466 (A) Estimates of the maximum proportion reduction of deaths from the baseline for
 1467 range of parameter estimates (point shows the estimate presented in the main analyses
 1468 and the ends show the upper and lower estimates for the parameter range) and (B)
 1469 estimates for how human rabies decreases proportional to the baseline as clinics are
 1470 added for these same parameter ranges (line shows the mean estimate presented in
 1471 the main analyses and the envelope shows the mean estimates for the parameters fixed
 1472 at the upper and lower range) for the two models (colors). See Fig S6.1A for ranges
 1473 used for each parameter.

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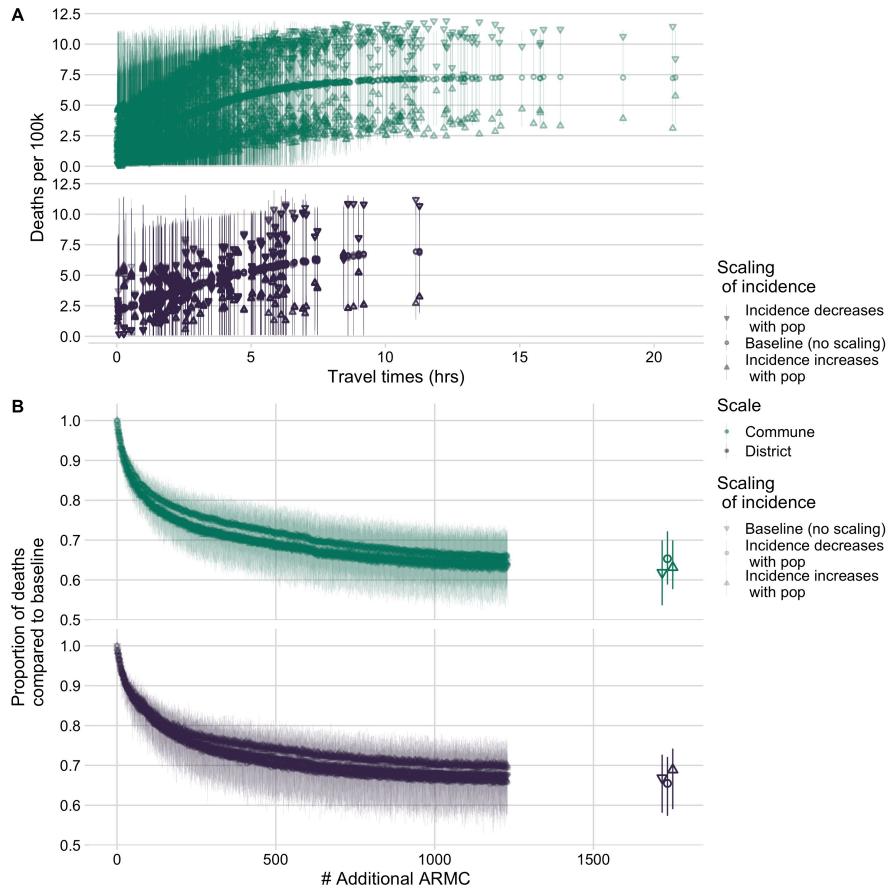


1477

1478 **Fig S6.3. Sensitivity analysis for vial demand.**

1479 (A) Estimates of the baseline vial demand for where each parameter was set to the
1480 upper and lower estimat of parameter estimates (point shows the estimate presented in
1481 the main analyses and the ends show the upper and lower estimates for the parameter
1482 range) and (B) estimates for how vial demand increases as clinics are added for these
1483 same parameter ranges (line shows the mean estimate presented in the main analyses
1484 and the envelope shows the mean estimates for the parameters fixed at the upper and

1485 lower range) for the two models (colors) for the two models (colors). See Table S6.1 & 2
1486 for ranges used for each parameter.



1487

1488 **Fig S6.4. Sensitivity analysis for exposure scaling with population.**

1489 Predicted relationship between (A) travel times and rabies death incidence per 100k
1490 persons and (B) the proportional reduction in deaths from the baseline as clinics are

1491 added for the district model vs. commune models (colors) with columns comparing the
1492 baseline (presented in main analyses) and assumptions of rabies exposure incidence
1493 increasing or decreasing with human population size (shapes). The points show the
1494 mean estimates from 1000 simulations and the line ranges show the 95% prediction
1495 intervals.

1496 **S7. Software citations**

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