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32

## 33 **Abstract**

### 34 **Background**

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

### 41 **Methodology & Principal Findings**

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

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

## **Conclusions & Significance**

PEP is effective at preventing rabies deaths, and in the absence of strong surveillance, targeting underserved populations may be the most equitable way to provision PEP. Given the potential for countries to use Gavi funding to expand access to PEP in the coming years, this framework could be used as a first step to guide expansion and improve targeting of interventions in similar endemic settings where PEP access is geographically restricted and baseline data on rabies risk is lacking. While better PEP access should save many lives, improved outreach, surveillance, and dog vaccination will be necessary, and if rolled out with Gavi investment, could catalyze progress towards achieving zero rabies deaths.

## **Author Summary**

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

in Madagascar. We find that PEP currently averts around 800 deaths each year, but that the burden remains high (1000 deaths/ year), particularly in remote, hard-to-reach areas. We show that expanding PEP availability to more clinics could significantly reduce rabies deaths in Madagascar, but our results reaffirm that expansion alone is will not achieve the global goal of zero human deaths from dog-mediated rabies by 2030. Combining PEP expansion with outreach, surveillance, and mass dog vaccination programs will be necessary to move Madagascar, and other Low- and Middle-Income countries, forward on the path to rabies elimination.

## Introduction

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

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

In 2015, a global framework to eliminate deaths due to canine rabies by 2030 ('Zero by 30') through a combination of PEP provisioning and dog vaccination was established by the World Health Organization (WHO) and partners [10]. Furthermore, in 2018, Gavi, the Vaccine Alliance, added human rabies vaccines to their proposed investment portfolio [11]. From 2021, Gavi-eligible countries should be able to apply for support to expand access to these vaccines, with potential to greatly reduce deaths due to rabies.

A primary challenge in expanding access effectively is the lack of data on rabies exposures and deaths in humans and incidence in animals in most rabies-endemic

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

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

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

## **Methods**

### **Estimating geographic access to PEP**

To estimate mean and population weighted travel times to the nearest clinic, we used two raster datasets: 1) the friction surface from the Malaria Atlas Project [18] at an  $\sim 1$  km<sup>2</sup> scale (Fig S1.1A) and 2) the population estimates from the 2015 UN adjusted population projections from World Pop ([19], originally at an  $\sim 100$ m<sup>2</sup> resolution, Fig S1.1B), which we aggregated to the friction surface.

From GPS locations of the 31 clinics that currently provision PEP, we estimated the travel time to the nearest clinic at an approximately 1 x 1 km scale as described in [18]. We then extracted the mean and population-weighted mean travel times for each district (2nd level administrative division, N = 114) and commune (the administrative unit below the district, N = 1579), and Euclidean distance, i.e. the minimum distance from the administrative unit centroid to any clinic. We used shapefiles from the UN Office for the Coordination of Humanitarian Affairs for the district and communes boundaries (as of October 31, 2018). To see which metric best predicted ground-truthed travel time data, we compared travel times and distance estimates to driving times collected by IPM during field missions, i.e. time it took to travel by car between two locations excluding break times (N = `nrow(ttime_driving)`), and patient reported travel times from a subset



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

### **Estimating bite incidence**

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

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

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

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

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

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

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

$$y_i = \text{Poisson}(\mu_i)$$

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

$$\mu_i = \sum_{j=1}^j e^{(\beta_t T_j + \beta_0)} P_j$$

As travel times are correlated with population size (Fig S3.1), we also compared how well bites were predicted by population size alone, and in combination with travel times. For the models with population size, we removed the offset and used either population 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 predictors.

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

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

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

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 a Bayesian regression framework via MCMC using the R package ‘rjags’ [21]. We used model estimates to generate fitted and out-of-fit predictions, and examined the sensitivity of estimates to adjustments for under-submission of forms (Supplementary Appendix, section S3).

## **Modeling human rabies deaths**

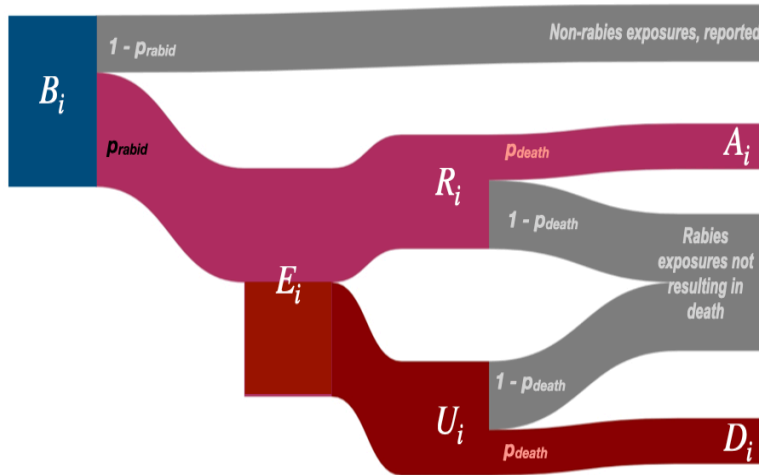
We estimate rabies deaths as a function of the number of bites predicted by our model and estimates of endemic rabies exposure incidence using an adapted decision tree framework. Table 1 lists all parameter values and their sources. Fig 1 describes how these parameters are used in the decision tree and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

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

213

Parameter	Value	Description	Source
$B_i$	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 <sup>1</sup>	[15]
$\rho_{max}$	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]

- 214 • <sup>1</sup>  $p_{rabid}$  is constrained so that rabid reported bites cannot exceed the total expected  
215 number of rabies exposures ( $E_i$ ) or maximum reporting in a given simulation ( $\rho_{max}$ ).



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

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

For  $E_i$ , we center the distribution at the lower end of our estimated exposure incidence from the Moramanga District (42 exposures/100,000 persons), with a range applied assuming 1% rabies incidence in dogs (estimated across a range of human-to-dog ratios between 5 - 25) and that on average a rabid dog exposes 0.39 persons [4] (see Fig S4.1). As there is little data on dog population size and human exposure incidence

in Madagascar[16,23], the range we used encompasses both observed human-to-dog ratios across Africa [14,24] and recent subnational estimates from Madagascar [25], and generates similar exposure incidences as observed previously across Africa [26,27]. Given previously high observed compliance in Madagascar [15], we assume that all rabies exposed patients who report to a clinic receive and complete PEP, and PEP is completely effective at preventing rabies.

### **Estimating the impact of expanding PEP provisioning**

We developed a framework to rank clinics by how much their PEP provision improves access for underserved communities, estimating incremental reductions in burden and increases in vaccine demand. Specifically, we aggregated our model-predicted estimates of annual bites to the clinic level. As multiple clinics may serve a single district or commune, we allocated bites to clinics according to the proportion of the population in each administrative unit which were closest. For each clinic, we simulate throughput by randomly assigning patient presentation dates, and then assume perfect compliance (i.e. patients report for all doses) to generate subsequent vaccination dates. We use these dates to estimate vial usage given routine vial sharing practices in Madagascar [15], but assuming adoption of the WHO-recommended abridged intradermal regimen (2 x 0.1 ml injections on days 0, 3, and 7 [28]). For both burden and vial estimates, we take the mean of 1000 simulations as each clinic is added.

We simulate expansion first to each district (N = 114) and then to each commune in the country for all communes with a clinic. We select the primary clinic (primary health facility, usually with capacity to provision vaccines) in the highest density grid cell of the

administrative unit as candidates for expansion. For the 85 communes without a primary clinic, we chose the secondary clinic (secondary health facility, often without formal vaccination capacity) in the highest density grid cell. 94 communes lacked any health facilities. Finally, we explore a scenario where all additional primary clinics (totaling 1733) provision PEP.

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

### **Sensitivity analysis**

To test the effect of our model assumptions on estimates of rabies burden and vial demand, we did a univariate sensitivity analysis of both parameters from the models of bite incidence and the decision tree (see Table S6.1 & S6.2 for parameter ranges used). We also examined how systematic variation in rabies incidence with human population size affected burden estimates. Specifically, if human-to-dog ratios are positively correlated with human populations (i.e. dog ownership/populations are higher in more

populated, urban areas), we might expect higher rabies exposure incidence as population size increases. Alternatively, if human-to-dog ratios inversely correlate with population size (i.e. dog ownership is more common in less populated, rural areas), we might expect exposure incidence to scale negatively with population size. We use scaling factors to scale incidence either positively or negatively with observed population sizes at the district and commune levels, while constraining them to the range of exposure incidence used in the main analyses (15.6 - 76 exposures per 100,000 persons, Fig S4.2) and simulated baseline burden, as well as expanded PEP access.

## **Data and analyses**

All analyses were done in R version 4.0.2 (2020-06-22) [29] and using the packages listed in the supplementary references (Supplementary appendix, section S7). All processed data, code, and outputs are archived on Zenodo (<http://doi.org/10.5281/zenodo.4064312> and <https://doi.org/10.5281/zenodo.4064304>), and maintained at <https://github.com/mrajeev08/MadaAccess>. The raw bite patient data at the national level are maintained in two secure REDCap (project-redcap.org) databases, one for IPM and another for all peripheral clinics provisioning PEP. These databases were last queried on September 19, 2019 for these analyses. The IPM GIS unit provided the data on geolocated clinics across the country. Anonymized raw bite patient data and full data on geolocated clinics are available from IPM following institutional data transfer protocols. Anonymized raw data collected from the Moramanga District were retrieved from the Wise Monkey Portal



(wisemonkeyfoundation.org) on the same date and are shared in the archived repository.

## **Ethics statement**

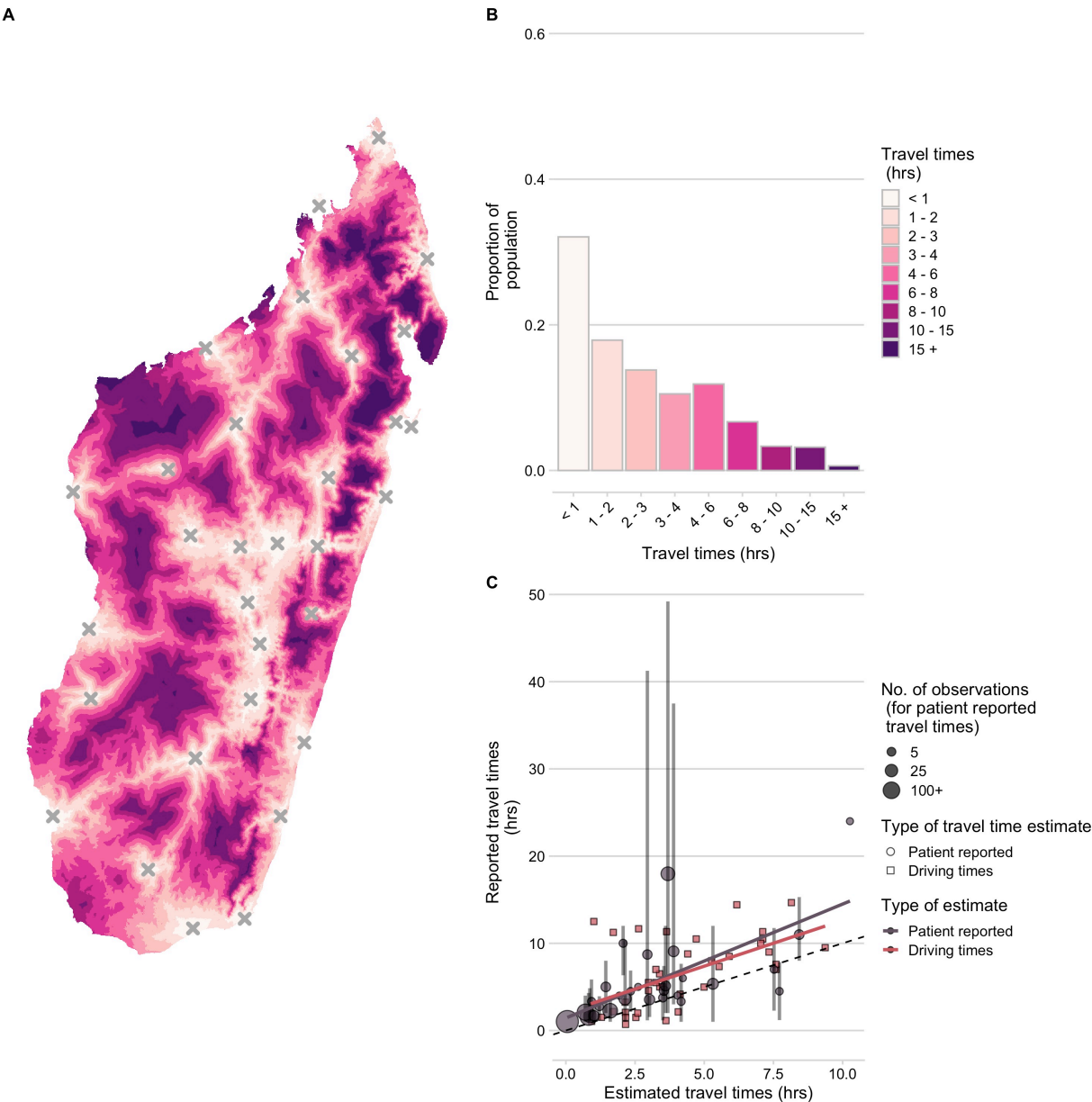
Data collection from the Moramanga District was approved by the Princeton University IRB (7801) and the Madagascar Ministry of Public Health Ethics Committee (105-MSANP/CE). Oral informed consent was obtained from all interviewed participants. Data collected from bite patients at the national level are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

## **Results**

### **Estimates of travel times to clinics are high and variable across Madagascar.**

Based on the estimates from the friction surface, approximately 36% of the population of Madagascar are estimated to live over 3 hours from a clinic (Fig 2). However, we found that these estimates underestimated both driving times across the country and patient-reported travel times to the Moramanga PEP clinic (Fig 2C). Patient reported travel times were highly variable for a given commune compared to the estimated travel times (Fig S1.2), potentially due to the fact that the friction surface assumes that the fastest available mode of transport is used across each grid cell (i.e. the presence of a road indicates that all travel through that grid cell is by vehicle). However, patients reported using multiple modes of transport, with some individuals walking days to the Moramanga PEP clinic (Fig S1.3).

318 While the travel time estimates may not reflect exact distributions of travel times, they  
319 were correlated with ground-truthed driving and patient-reported times and likely reflect  
320 patterns of access over the country (Fig 3C, Fig S1.4). Travel times weighted by  
321 population at the grid cell level were a better predictor than unweighted travel times or  
322 distance ( $R^2 = 0.43$ , Table S1.1), therefore, we use population-weighted travel time as a  
323 proxy for access at the commune/district level in subsequent analyses.



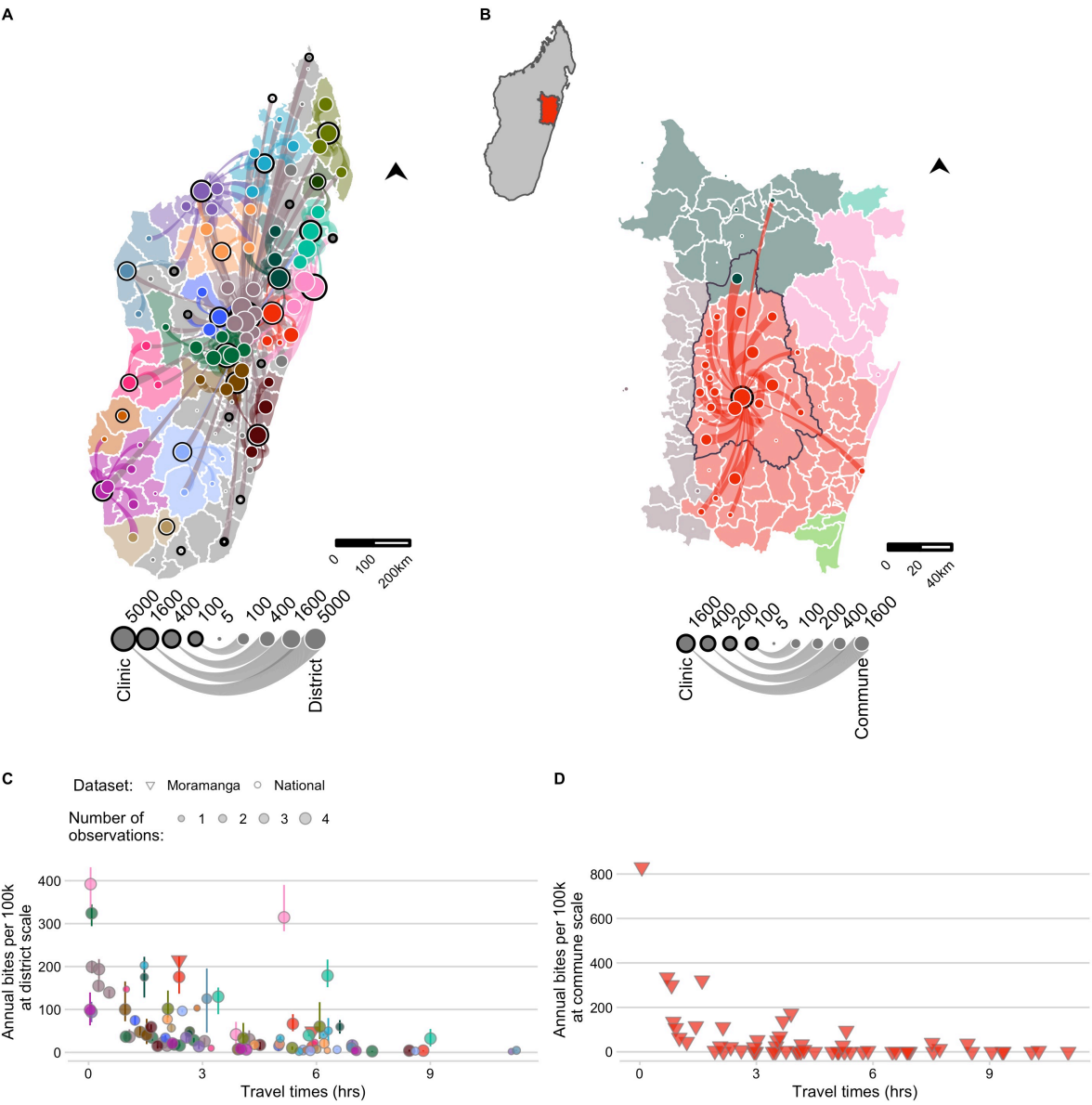
**Fig 2. Travel times to clinics provisioning PEP across Madagascar.**

(A) Estimated at an  $\sim 1 \text{ km}^2$  scale. (B) Distribution of the population across travel times. (C) Correlation between ground-truthed travel times (mean of patient reported travel times to the Moramanga PEP clinic at the commune level and reported driving times between GPS points) and friction surface travel time estimates. The vertical lines show the 95% quantiles for reported travel times and the point size shows the number of observations for each commune. The best fit lines (red and grey) from a linear model where observed travel times are predicted by estimated travel times for each data source are also shown. The dashed black line is the 1:1 line.

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

Bite incidence estimates generally increased with decreasing weighted travel times at both administrative scales (district and commune), although there was considerable variation between catchments for the magnitude of this relationship (Fig 3C and D). After additionally excluding any year with less than 25% of forms submitted, our final dataset consisted of estimates of average bite incidence for 83 of 114 districts (Fig 3C), and 58 communes within the catchment of the Moramanga District (Fig 3D, see Supplementary Appendix section S2 for more details). 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

346 estimates, when aggregated to the district, bite incidence estimates fell within the  
347 ranges observed from the national dataset.



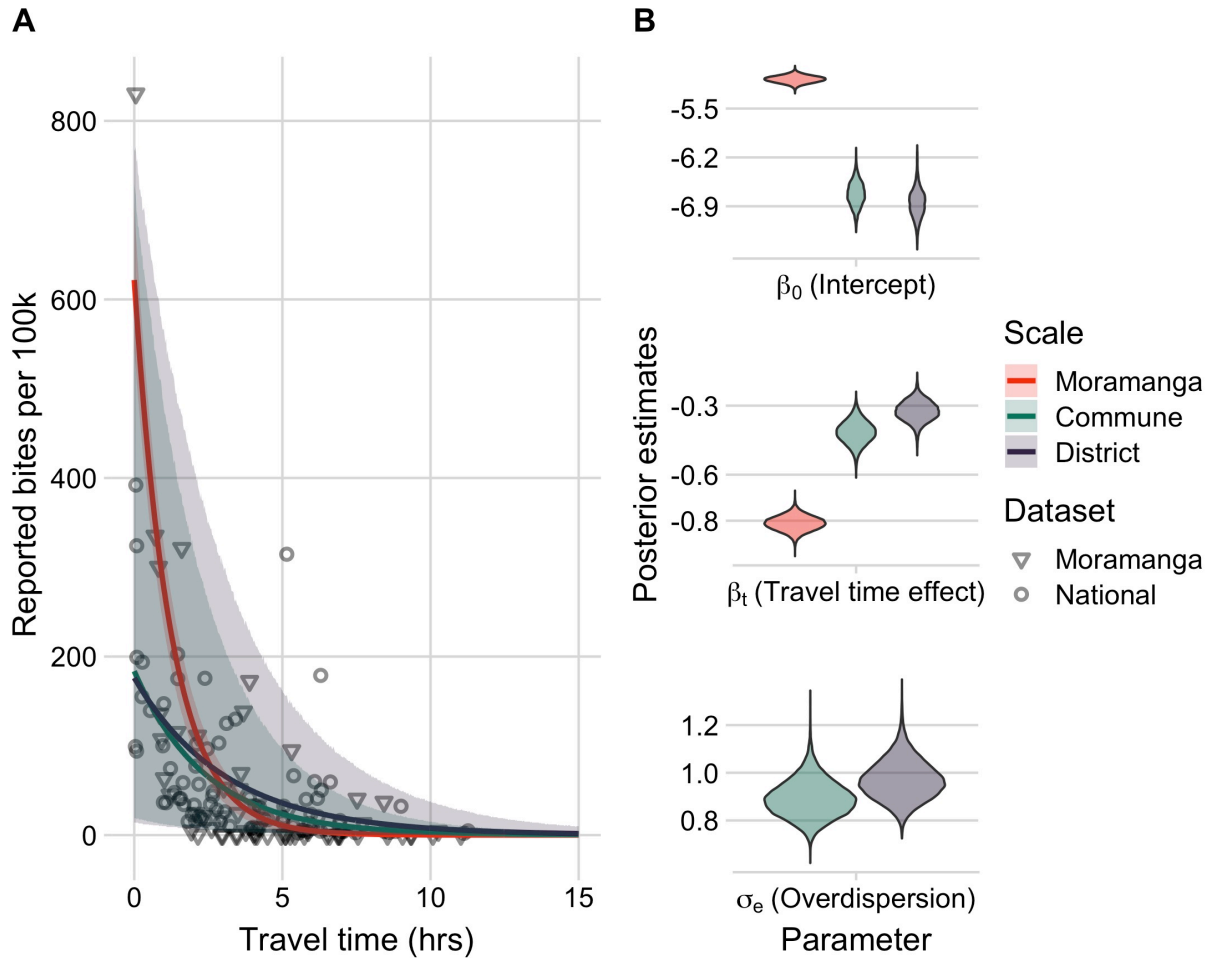
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**Fig 3. The network of patient presentations and estimates of annual bite incidence.**

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

Our modeling results show that travel times were a strong and consistent predictor of reported bite incidence in both datasets and across scales with the best fitting models including travel times and an overdispersion parameter (Fig 4, see Supplementary

372 Appendix section S3 for comparisons to models with catchment effects and with  
373 population size as a covariate). As the predictions of the model fit to the Moramanga  
374 data without accounting for overdispersion fall within the prediction intervals for the  
375 models fit to the national data (Fig 4A), for subsequent predictions, we used the  
376 parameter estimates from models fit to the national data, which encompass the range of  
377 travel time effects observed in our datasets. Moreover, our out-of-fit predictions to the  
378 data across scales suggest that the commune model is able to capture travel time  
379 impacts at the commune level (Fig S3.3), therefore we use both the district and  
380 commune model to disaggregate burden to the finest scale possible. Finally, we  
381 examined the sensitivity of models to how we corrected for underreporting of data and  
382 found that parameter estimates of travel time impacts were similar across models and  
383 performed similarly in prediction (Fig S3.8 and Fig S3.9).



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

(A) The estimated relationship between travel time in hours (x-axis) and mean annual reported bite incidence (y-axis). The lines are the mean estimates and the envelopes are the 95% prediction intervals generated by drawing 1000 independent samples from the parameter posterior distributions for three candidate models: model with travel times at the 1) commune- and 2) district-level fitted to the national data with an overdispersion parameter ( $\sigma_e$ ) and 3) travel times at the commune level fitted to the Moramanga data with a fixed intercept and unadjusted for overdispersion. The points show the data: National data (circles) at the district level used to fit the District and Commune models,

and Moramanga data (triangles) at the commune level used to fit the Moramanga model. (B) The posterior distribution of parameters from the respective models for the model intercept, travel time effect, and for overdispersion (national data only).

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

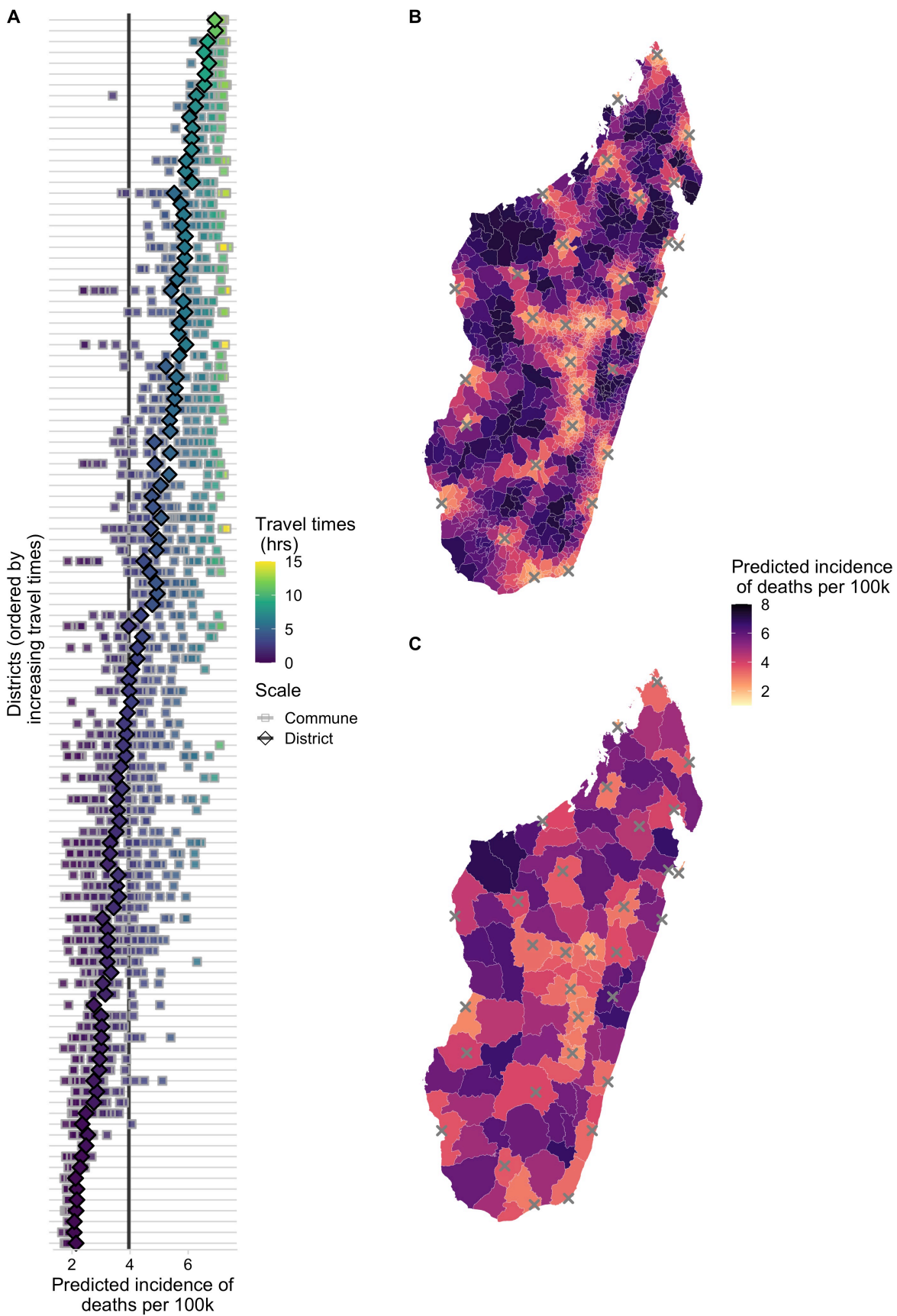
In general, the incidence of rabies deaths increases with travel times to clinics, and there is significant sub-national variation when deaths are modeled at the district and commune scale, with the least accessible communities having most deaths (Fig 5B & C). We estimate that under the current system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

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

Model	Reported bite incidence per 100k	Burden of deaths	Deaths averted by current PEP provisioning
Commune	85 (56 - 129)	963 (795 - 1118)	801 (644 - 968)



District	85 (52 - 136)	958 (752 - 1156)	807 (609 - 1005)
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**Fig 5. Spatial variation in predicted incidence of human rabies deaths per 100,000 persons.**

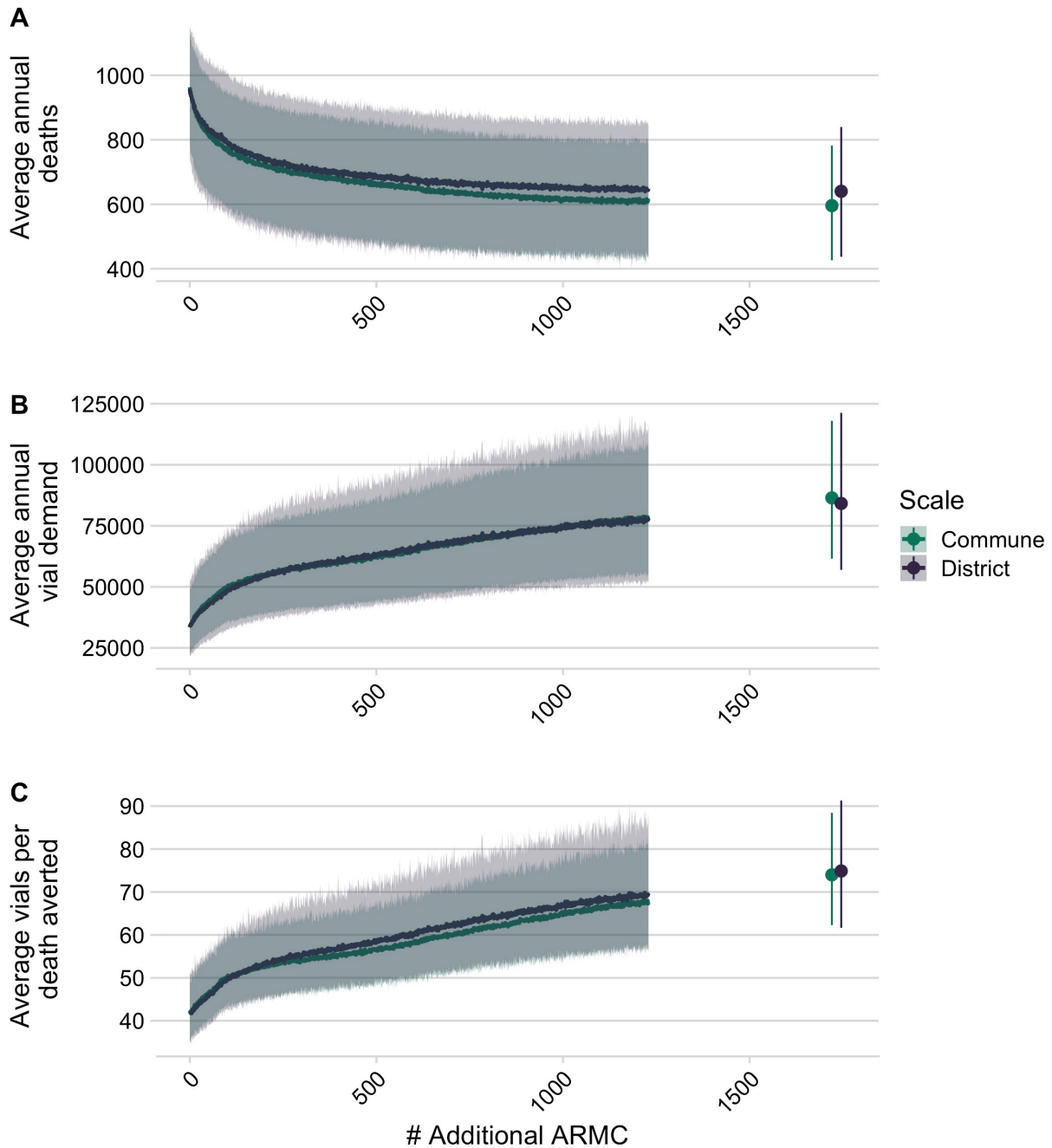
(A) for each district (y-axis) in Madagascar. Diamonds show the predicted incidence for the district model and squares show predicted incidence for the commune model fit to the National data for all communes in a district. Points are colored and districts ordered by travel times. The vertical lines show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

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

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

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

436 Vial demand also outpaces reductions in burden (Fig 6B), with more vials needed per  
437 death averted (Fig 6C). Our model predicts an increase from 33500 vials (95% PI:  
438 22900 - 49400) per annum under current provisioning but with the abridged intradermal  
439 regimen (i.e. visits on days 0, 3, 7), to ~56900 vials (95% PI: 40200 - 77800) with 250  
440 clinics providing PEP, and ~86400 vials (95% PI: 61600 - 118000) if all primary clinics  
441 provision PEP. In these scenarios, clinic catchment populations and throughput  
442 decrease, with clinics seeing fewer patients per day (S5.6).



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

(A) Decrease in deaths due to rabies, (B) increase in total # of vials as additional clinics provisioning PEP are added at the national level, and (C) increase in vials needed per

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

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

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

## Discussion

### Main findings

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

### Limitations

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

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

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



513 burden estimates [22]. Likewise, we do not account for differential risk for severely  
514 exposed patients not receiving Immunoglobulins (RIG), which is only available at IPM in  
515 the capital of Antananarivo, but recent studies show that even in the absence of RIG,  
516 PEP is extremely effective [4]. We also assume that clinics reliably provision PEP, but a  
517 2019 KAP survey reported clinics experiencing stock-outs [25].

518 We assumed geographic access to PEP was the primary driver of health-seeking  
519 behavior, but socioeconomic status, education and awareness about rabies [[33]; [27];  
520 [34]; [35]; castillo2020behavioral] all play a role. For example, most PEP clinics also  
521 charge fees (from 0.50 - 3.00 USD for consultations, wound treatment, etc. [25]) which  
522 may also act as barriers to PEP access. In Madagascar, where PEP is free-of-charge,  
523 the main cost to patients is transport and time lost. More remote communities tend to be  
524 of lower socioeconomic and educational status [2], so travel time may be a proxy for  
525 these correlated variables. Significant overdispersion in the data that cannot be  
526 explained by travel times suggests that clinic-level variation (e.g. vaccine availability and  
527 charges) and regional differences (e.g. dog populations, outbreaks, awareness) further  
528 influence health-seeking behavior and vaccine demand. Although our estimates could  
529 be improved with better data on rabies incidence, health-seeking behavior, and PEP  
530 provisioning, predicting PEP impacts will remain challenging given the complex  
531 interactions between socioeconomic factors, access to and quality of care, and human  
532 behavior, as illustrated by the case studies in Box 1. However, it is very likely that the  
533 impacts of improving access to PEP could be further increased with outreach and  
534 awareness raising efforts that we were unable to parameterize.

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

1. Anosibe An'ala District (population ~ 100,265), south of Moramanga, has moderate incidence of bite patients (~ 54/100,000 persons) even though travel times often exceed 24 hours. While a road connects the main Anosibe An'ala commune to the Moramanga PEP clinic, it is only passable by large trucks during much of the rainy season, with speeds usually < 10km per hour. Over 9% of patients from Anosibe An'ala had been in close proximity or touched a person that died from rabies (four suspect human rabies deaths of patients who did not receive any PEP), whilst of patients with Category II and III exposures that were interviewed, 11/19 (58%) were bitten by probable rabid dogs. Given the high travel times (although underestimated by the friction surface) and incidence of reported rabies exposures and deaths, we predict a large but unobserved rabies burden in this remote community (~6.02 deaths per year) and we ranked a clinic provisioning PEP in Anosibe An'ala 28th for travel time reductions. Other remote communities likely experience similar high and unrecognized burden, but improved surveillance is necessary to identify such areas. Notably, bite patients in this district demonstrate willingness to travel for free PEP (in some cases walking 3 days to a clinic) with awareness of rabies risk. Community outreach and active surveillance in other remote areas could also greatly improve people's awareness of risk and health seeking behavior.
2. Recently, a middle-aged taxi driver died of rabies in suburban Antananarivo. The day after being bitten by an unknown dog, he reported to a clinic that referred him to the closest clinic provisioning PEP, approximately one hour's drive from his home. His family urged him to go, but he did not believe his risk was high and decided not to seek further care. He developed symptoms two weeks later and was confirmed as a rabies death by the National Rabies Reference Laboratory. Despite prompt reporting, appropriate referral, and socioeconomic indicators suggesting a high care-seeking probability, this person did not receive PEP. His story highlights the need for sensitization about rabies, how PEP provisioning at

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

## **Broader context**

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

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

586 We predict that as clinics are expanded, throughput (daily patients reporting to a clinic)  
587 will decrease. This may complicate the supply chain and make provisioning PEP more  
588 challenging as vial demand becomes less predictable, leading to stock outs or wastage.  
589 Decentralized provisioning mechanisms, for example adopting routine childhood  
590 vaccine supply chains, or novel vaccine delivery methods such as drones [48], may  
591 mitigate these challenges. When nerve tissue vaccines were used in Madagascar,  
592 clinics requested vaccines upon demand and PEP access was more widespread, but  
593 provisioning the more expensive cell culture vaccines to all clinics became too costly  
594 [16]. Widespread vaccine provisioning is therefore feasible given Madagascar's health  
595 infrastructure, if cost barriers are removed.

596 Gavi investment could greatly reduce the access and cost barriers to PEP [6,7,22,49].  
597 Currently, each clinic in Madagascar serves an average catchment of 780,000 persons.  
598 Latin American countries, where significant progress has been made towards  
599 elimination, aim for one PEP clinic per 100,000 persons. In Madagascar this would  
600 require around 212 additional clinics provisioning PEP. We predict that Gavi investment  
601 would be highly cost-effective, greatly reducing deaths by expanding PEP supply to  
602 underserved areas.

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

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

## **Conclusion**

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

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