Redefining snakebite envenoming as a zoonosis: disease incidence is driven by snake ecology, socioeconomics and anthropogenic impacts

Authors

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Abstract

Snakebite is the only WHO-listed, not infectious neglected tropical disease (NTD), although its eco-epidemiology is similar to that of zoonotic infections: envenoming occurs after a vertebrate host contacts a human. Accordingly, snakebite risk represents the interaction between snake and human factors, but their quantification has been limited by data availability. Models of infectious disease transmission are instrumental for the mitigation of NTDs and zoonoses. Here, we represented snake-human interactions with disease transmission models to approximate geospatial estimates of snakebite incidence in Sri Lanka, a global hotspot. Snakebites and envenomings are described by the product of snake and human abundance, mirroring directly transmitted zoonoses. We found that human-snake contact rates vary according to land cover (surrogate of occupation and socioeconomic status), the impacts of humans and climate on snake abundance, and by snake species. Our findings show that redefining snakebite as zoonosis provides a mechanistic eco-epidemiological basis to understand snakebites, and the possible implications of global environmental and demographic change for the burden of snakebite.

Introduction

Snakebite envenoming causes acute life-threatening disease with long lasting consequences for survivors [1]. By most recent estimates, up to 1.8 million people suffer from snakebite envenoming every year, of which 20,000 – 94,000 die of the resulting illness [2]. Such a high burden is increasingly recognised as a global health crisis and, in combination with its relative neglect from a research perspective, has led to snakebite’s recent inclusion on the WHO list of class A neglected tropical diseases (NTDs) [3], a first for a non-infectious disease, and to the development of a global action plan to reduce its burden [4].
Mathematical modelling has been useful for identifying processes that affect the incidence of NTDs and managing them to reduce their burden [5,6]. For instance, modelling revealed that only treating confirmed cases of lymphatic filariasis while neglecting vector and alternative host populations facilitated low-level endemic persistence and the evolution of drug resistant parasites, which together hampered long-term mitigation (reviewed in [7]). Models have also been instrumental for testing and implementing interventions for rabies [8]. The spillover of rabies from its zoonotic mammalian host, mostly as a result of a bite from an infected canine, is a relatively simple transmission process that can be represented with epidemiological models.

Rabies, the above example, and snakebite envenoming have some striking similarities. That is, a pathogenic agent - venom - is transmitted to humans after a contact event with a vertebrate host. Despite this similarity, mathematical models of snakebite are scarce (but see [9]), limiting the extent to which mitigation strategies can be assessed prior to field implementation, for example. In contrast, pharmaceutical solutions still dominate mainstream snakebite mitigation and research agendas (e.g., Snakebites: making treatments safe, effective and accessible | Wellcome; [10]). The snakebite roadmap aims to reduce the number of snakebite deaths and disabilities by 50% by 2030 [11], and identifies novel methods and tools to better understand snakebite epidemiology as a priority to help achieve this goal. Improved epidemiological models for snakebite could fill a major current void in understanding snakebite, improving mitigation efforts and maximising the efficacy of post-bite treatment systems (e.g., directing antivenom supplies efficiently) [5,12].

Mechanistic representation of zoonotic spillover predicates that transmission depends on three major principles [13,14]: 1) reservoir and spillover hosts coinciding in time and space (e.g. [15]), 2) the disease prevalence and/or pathogen shedding in reservoir hosts depending on the contact route necessary (e.g. [16]), and 3) the spillover host developing disease when it
is infected. Risk mapping studies of snakebites indicate that there are analogous factors relating to these mechanisms for zoonotic spillover. First, models of snake distribution and abundance, and maps of human population density can be used to represent human-snake spatial [17,18] and temporal [19] alignment, which underlies human-snake contact. Second, the equivalent of pathogen prevalence (i.e., possessing venom) is 100% among venomous snakes, hence the likelihood of transmission (envenoming) is rather a function of how likely it is that venom is delivered during a bite (as opposed to dry bites), which varies considerably between venomous species [20]. And third, host susceptibility relates to the effect of venoms on the human body [21].

Exposure factors and post exposure vulnerabilities (e.g. occupational, cultural and socioeconomic) may mediate these steps to further influence outcomes and ultimately the overall burden in a population [22–24]. For instance, working in agriculture could increase spatio-temporal alignment; poverty could limit the use of protective clothing to influence the probability of envenoming given a bite; and cultural differences could influence healthcare seeking behaviour, which could determine the toll on the body during an envenoming event.

Figure 1, following Plowright et al.,’s [13] framework for zoonotic spillover, represents such a conceptual arrangement as a sieve that starts with snake diversity, distribution, abundance, behaviour, venom toxicity, and its overlap with humans and individual risk/susceptibility factors.

Whereas the majority of NTDs comprise transmission of a pathogenic microorganism (or a complex of microorganism species e.g., *Leishmania spp.*) from one or more reservoir and/or vector hosts to humans, the transmission dynamics of snakebite involve envenoming of humans (or other victim, such as livestock) from one or more venomous snake (‘reservoir’) species. In systems in which only one species dominates the snakebite burden, an appropriately simple single-species model has been shown to successfully predict the
geographical variability of snakebite incidence. For instance, Bravo-Vega et al. [9] modelled
the frequency of encounter with *Bothrops asper* as a function of environmental suitability to
predict snakebite incidence in Costa Rica. However, such models have not been applied in
settings where multiple species bite and influence variability of snakebite envenoming
incidence in space and in time. For example, the ‘big four’ species considerably shape the
burden of snakebite envenoming in South Asia [25], while Goldstein et al. [26] show that
burden dynamics can be complex over time due to the influence of multiple biting species and
the environment on the behaviour of both humans and snakes.

In the present study, we sought to capitalise on recent snakebite research developments in
incidence mapping [23], snake distributional ecology [18], and zoonotic spillover theory [13]
to develop a novel mechanistic epidemiological framework representing the biological
components of snakebite. Specifically, we explored the extent to which various types of
models typically applied to directly transmitted infectious diseases explain the geography of
snakebite and envenoming incidence estimates. We use the island nation of Sri Lanka, a
snakebite hotspot, as a model system given that, as of the time of writing, it is the only high
snakebite burden region for which high quality/high resolution country-wide data exist to
formulate, test and compare models on snakebite and envenoming incidences. In addition to
demonstrating successful risk mapping, we show that geographical patterns of incidence arise
from dynamic environmental socio-ecological processes that include effects of climate,
occupational risk factors, land use and its changes and direct human impacts on snake
populations. Recasting snakebite as a zoonosis and formally applying conventional
epidemiological models provides a novel way forward in understanding snake bite
epidemiology, which in future studies will allow us to better anticipate risks and potentially
help achieve ambitious mitigation targets [11] in a rapidly changing world.

**Methods**
We first identified a series of mathematical formulations for human-snake contacts to represent snakebite as a zoonotic disease transmission process. In conventional infectious disease transmission models, disease spread is considered to be frequency-, density-dependent or a mixture of both. When frequency-dependent, the per-capita rate at which susceptible individuals become infected depends on pathogen prevalence in the population. When density-dependent, transmission increases with infected host density. For snakebites, pathogen prevalence for a given reservoir is 100% (all individuals of a venomous species carry venom; Figure 1), and as such we discarded all frequency-dependent formulations. The remaining density-dependent contact formulations (Table 1) summarise different mixing dynamics between humans and snakes, resulting in functional relationships between snake abundance and snakebite incidence that range from linear to asymptotic to bell-shaped [27].

To test the models' abilities to explain snakebites, we transformed them from continuous to discrete time, and estimated their parameters regressing the estimated snakebite and envenoming incidence rates from Ediriweera et al. [23] against each functional relationship. As Ediriweera et al. [23] estimates are spatially explicit we first fitted a model ignoring the spatial component, and then we fitted the same models with a conditional autoregressive random effect.

Data

Data used for fitting and testing models and estimating parameters were two published datasets (rasters) of the spatial distribution of snakebite and envenoming incidence rates, estimated with model-based geostatistics applied to a country-wide community survey of ~0.8% of the Sri Lankan population [23], under the assumption that these estimates represent the ground truth. The response variables for regressing the functional relationships were the number of snakebite and envenoming cases, respectively, found by multiplying the mapped incidence rates by human population density (described below). The independent
data used to explain incidence rates and which represent the causal snakebite factors (Figure 1) were:

**Distribution and abundance of reservoir hosts**: raster images of the abundance patterns of the most medically relevant venomous snakes of Sri Lanka, estimated with point process models as functions of the environment (climate, topography and land cover), and adjusted for species’ relative abundances [28].

**Distribution and abundance of spillover hosts**: raster image of human population density raster layer from 2010 (closest point in time prior to the snakebite survey period of August 2012 – June 2013; [23]) obtained from the Gridded population of the world (GPW v4) hosted by the Socioeconomic Data and Applications Center (SEDAC, [https://sedac.ciesin.columbia.edu](https://sedac.ciesin.columbia.edu)).

**Spillover host exposure risk factors**: raster image of land cover representing the predominant classes forest, degraded forest, agriculture, urban and tea (see ‘Deriving land cover data’ below for source details). Land cover correlates well with socioeconomic status and predominant occupation [29], which are the primary human-related risk factors [22] and which in the model represent different risk categories via model parameters such as the human-snake contact rate.

**Data formatting**

Prior to analysis we homogenised and synchronised the resolution of all data to a common grid comprising 5 × 5 km pixels (25 km²) projected to the datum of Sri Lanka (SLD99, EPSG 5235). Synchronising data allowed matching data points to regress the number of snakebite and envenoming cases against human, snake and land cover data according to the model tested. A 5 × 5 km grid was chosen to facilitate computation and retain a reasonable degree of biological detail relevant to the study aims. Human population density and snake abundance estimates were upscaled from their original 1 km resolution by aggregation, summing the
values of adjacent cells by a factor of 5 grid cells along longitude and latitude. Snakebite and envenoming incidence layers were resampled from their original ~1.5 × 3 km to the target resolution using weighted bilinear interpolation. The land cover layer was upscaled from 30 m to 5 km by majority vote per pixel (land cover class was assigned to each grid cell based on the most common class among the ~27000 30 m grid cells contained in each 5 × 5 km pixel).

**Deriving land cover data**

The five categories considered for the analyses were derived using unsupervised isoclustering and visual interpretation of remotely sensed data for the year 2010 (Landsat surface reflectance, original Landsat optical bands and NDVI). The resulting 30 m land cover maps were validated using 600 randomly generated points across Sri Lanka, with which we estimated a classification accuracy of >95%.

**Functional relationships for human-snake contacts**

The simplest formulation of human-snake contact is the mass action model, whereby the total number of possible different contacts is found by \( \text{No. Humans} \times \text{No. Snakes} \). This formulation is widely used for zoonotic transmission, and the simplest model relevant to snakebites is the susceptible-bitten model \([30]\). Here, the growth of bitten humans \((H_b)\) per time unit \((dH_b/dt)\) is proportional to the number of possible contacts between susceptible humans \((H_s)\) snakes \((S)\):

\[
\frac{dH_s}{dt} = -\beta H_s S \quad (1.1)
\]

\[
\frac{dH_b}{dt} = \beta H_s S \quad (1.2)
\]

where \(\beta\) is the human-snake contact rate. This model assumes that time is continuous, however snakebite incidence data has a resolution of one year, for which discrete-time models are more adequate. The continuous (left) and discrete-time (right) models for snakebite based on the SB model are:
\[
\frac{dH_s}{dt} = -\beta H_s S \Rightarrow H_{s,t+1} = H_{s,t} - H_{s,t} \exp(-\beta S) \quad 1.3)
\]

\[
\frac{dH_b}{dt} = \beta H_s S \Rightarrow H_{b,t+1} = H_{b,t} + H_{s,t} (1 - \exp(-\beta S)) \quad 1.4)
\]

The tested human-snake contact formulations are given in Table 1 in their original and discretised forms. We held no a priori reason to favour one model over another, so we explored all of their relative abilities to explain snakebite and envenoming incidence.

**Model implementation and selection**

Ediriweera et al., [23] report both snakebite and snakebite envenoming incidence nationally for Sri Lanka, which here we refer to as two measures of risk, Snakebite and Envenoming. The former represents all confirmed contacts with snakes with and without envenoming, and the latter are the contacts which resulted in envenoming illness. To model envenoming we used two approaches. First, we modelled snakebite as a contact process with the functional relationships and assumed that envenoming is a subset or secondary event, whose probability of occurring was another function of snake abundance. Second, we treated envenoming cases alone in the same way we treated snakebites (see below).

To estimate model parameters we regressed the number of snakebite or envenoming cases against the functional relationships (Table 1) using Markov Chain Monte Carlo (MCMC) sampling in JAGS [31]. Prior to implementation, the contact processes (Table 1, column 1) were transformed from their continuous-time form into discrete-time, representing the probability that there were any snakebites during the study period \((t, t+1)\). The discrete-time form of equation 1.4 to represent snakebite incidence is [32]:

\[
H_{b,t+1} - H_{b,t} = H_{s,t} \times (1 - \exp(-\beta S)) \quad 2.1)
\]

Therefore, the probability that there are any snakebites when during one year \((t, t+1)\) is:

\[
P(t,t+1) = \frac{H_{b,t+1} - H_{b,t}}{H_s} = 1 - \exp(-\beta S)
\]
To summarise, after taking $H_s$ from the right to the left hand side of the equations, snakebite or envenoming incidence is proportional to a function of snakes and/or humans, $F(H, S) = P(t, t+1)$. More generally the number of snake-bitten people is:

$$H_b = H_s \times P(t, t+1)$$

To select a more appropriate model in the MCMC sampling process we treated snakebite and envenoming cases as either Poisson:

$$H_b^* \sim \text{Poisson}(H_b)$$

or Negative Binomial, parameterised by $P_N$ and dispersion parameter $r$:

$$r \sim \text{unif}(0, 50)$$

$$P_N = \frac{r}{r + H_b}$$

$$H_b^* \sim \text{NegBin}(P_N, r)$$

in order to use the best statistical distribution for the number of cases.

**Human-snake contact rates**

To estimate effects of the different snake species and human-related factors, the contact rate $\beta$ was decomposed into different aspects. The first aspect included the estimation of one contact rate per snake species, such that $S_t$ from equation 2.1, for instance is:

$$S_t = \sum B_s \times (A, E)_s \times S_s$$

the sum of the individual snake species abundances multiplied by their specific human-snake contact rates $B_s$, and species aggressiveness or envenoming-severity indices $[(A, E)_s]^{[28]}$. Each index was included depending on whether the contact process analysed was snakebite ($A_s$) or envenoming ($A_s \times E_s$). This means that the absolute magnitude of contact rate for snakebite is $B_s \times A_s$ and for envenoming is $B_s \times A_s \times E_s$. Thus $B_s$ represents other factors not
related to aggressive behaviour \( (A_s) \) or envenoming severity \( (E_s) \) that influence human-snake
interactions and their outcomes.

The second component of the decomposed contact rates are a series of functions of human
population density (number of people per grid cell) that attempt to adjust total snake
abundance in relation to humans, since high human population density is a well known
threatening process for biodiversity [33,34]. The functions of human population density were:

\[
\beta(H) = \begin{cases} 
\exp(\beta_0 + \beta_1 H) \\
\exp(\beta_0 + \beta_1 H^2) \\
\exp(\beta_0 + \beta_1 H + \beta_2 H^2)
\end{cases}
\]

In this approach, if \( \beta_0, 1, 2 \) coefficients are drawn from a normal distribution in the MCMC
sampling process it is possible to model the negative effect of humans on incidence, whilst
retaining a positive relationship between the total number of cases and human population
density since \( \beta(H) \) will always be positive. To estimate human susceptibility in the models we
categorised their parameters \( (\beta \text{ and } 2.2) \) in five land cover classes.

To summarise, we estimated parameters and measured the ability to represent snakebite and
envenoming of the models with and without the functions of human population density \( (2.2) \),
with and without its parameters categorised by land cover, and estimating a global \( \beta \) with and
without categorisation by land cover.

**Model of envenoming probability**

For the approach of treating envenoming as an event that follows a snakebite, we treated the
number of envenoming cases as the subset of snakebites that result in envenoming. Therefore,
the number of envenoming cases is:

\[
H_{\text{envenomed}} = H_b \times P_{\text{env}}
\]
where $H_{envenomed}$ is the number of envenoming cases and $P_{env}$ is the probability that a snakebite results in envenoming, which we derived from an expert-collated index of species’ envenoming severity (Table 2; [28]). To estimate $P_{env}$ we treated the number of envenoming cases as Poisson or Negative binomial, but estimated the probability logistically using two model-formulas:

\[
\log\left(\frac{P_{env}}{1-P_{env}}\right) = \sum B_s \times E_s \times S_s 3.1)
\]

\[
\log\left(\frac{P_{env}}{1-P_{env}}\right) = B_{LC} + \sum B_s \times E_s \times S_s^* 3.2)
\]

where, in both equations, $B_s$ is the statistical effect of snake species $s$, $E_s$ is the index of envenoming severity (Table 2) and $S_s^*$ is snake species $s$ after applying the correction of abundance in relation to humans ($\beta (H)$). In model formula 3.2, the term $B_{LC}$ is a random intercept for land cover class. The criteria to select one formula over the other was minimisation of the deviance information criterion (DIC) and convergence [35].

**Model selection**

We first implemented all functional relationship models and ran short MCMC chains of 10-50 K iterations to discard those with erratic sampling behaviour, poor chain mixing or consistently higher DIC than other functions. Once we obtained a more manageable subset of models we ran the full MCMC chains of up to 750,000 iterations and then checked for convergence with the Gelman diagnostic test [36]. With the latter we made sure that posteriors are unrelated to starting prior values (ratio of between and within chain variances should approach one). Finally, we analysed the spatial pattern and statistical distribution of the residuals by subtracting the median of posterior samples with snakebite and envenoming incidence data.

The criteria to select one functional relationship over another were: 1) ease of parameter estimation and convergence of MCMC chains; 2) adequate reproduction of the spatial pattern
of raw number of snakebites and envenomings and their annual incidence rates, by measuring
the spatial association of the predictions with a modified T-test for spatially autocorrelated
data [37]; 3) minimising the DIC; and 4) adequate representation of the statistical distribution
of the snakebite and envenoming data using quantile-quantile plots.

**Model with spatial effects**

To fit the models with spatial effects we used the mean and standard deviation estimates of
the non-spatial version as parameter priors for the main effects $\beta_0$, $\beta_1$, and $B_S$ to ease
convergence. Random effects for the above models were incorporated as a log-linear random
intercept for the number of predicted cases:

$$\log H_b = \log( H \times F(H, S)) + \rho_i$$

This means that $\rho$ was sampled from a conditional autoregressive normal distribution where
each $\rho_i$ is proportional to the average $\rho\cdot i$ of its immediate neighbours in a queen-type
neighbourhood. These final models were fitted with Nimble [38] instead of JAGS.

**Results**

The selected models reproduced well the magnitude and distribution of both snakebite and
envenoming incidence rates observed in Ediriweera et al., [23]. National snakebite and
envenoming incidence patterns were best predicted by first modelling snakebites with the
functional relationship based on simple mass action (Table 1) and then estimating the
probability that a snakebite results in envenoming using the land cover random-intercept
model (equation 3.2).

**Snakebites model**

Of the contact formulations listed in Table 1, the simple mass action ($\beta SH$) and refuge effect
on humans ($\beta S (H - S/q)$) were the best performing models, with the lowest deviance
information criterion (DIC; Table 1). The refuge effect model had lower DIC than the simple
mass action (Table 1) and higher correlation with the snakebites and incidence data (refuge
effect, $r = 0.67$, d.f. = 128, $P = 0$; simple mass action, $r = 0.61$, d.f. = 137; $P = 0$), suggesting at
face value a better fit. We considered that the remaining formulated models were all
unsuitable as we failed to obtain reliable parameter estimates due to lack of MCMC
convergence.

To select one model over another as the better one, we also took into account the statistical
distribution of predicted incidence rates. The statistical distribution of the incidence rates
produced by the refuge effect model was very different to the original incidence rate
distribution (Supplementary materials, Figure S1 and S2). Therefore, we chose the simple
mass action model. The number of snakebites and incidence patterns produced by this model
were qualitatively very similar and had a statistical distribution nearly identical to that of the
data.
Table 1. Disease transmission terms tested representing functional relationships between snakes and humans and resulting in snakebite. Each term has been previously applied in various settings for infectious disease studies so here we list only the earliest reference for each. DIC = deviance information criterion, pD = potential degrees of freedom, H = humans, S = snakes, β = contact rate. Missing DIC values means that we could not obtain a converged model, so DIC values were not comparable with those of converged models.

| Transmission term | Discrete time form $F(H, S, \theta)$ | Name and description | Source | DIC, pD* |
|-------------------|--------------------------------------|-----------------------|--------|----------|
| $\beta HS$        | $1 - \exp(-\beta S)$                | Simple mass action. $H \times S$ is the total number of possible contacts | [30]   | 17484, 20.02 |
| $\beta H p S^q$   | $1 - \exp(-\beta H^{p-1} S^q)$      | Power. Similar to mass action, but $p$ and $q$ take values 0, 1, and increase or decrease the number of contacts of $S$ in relation to $H$ and vice-versa. | [39]   | --- |
| $\beta (S - H/q_h)$ | $1 - \exp(-\beta (S/H - 1/q_h))$ | Refuge effect on $S$. Parameter $q$ represents the fraction of snakes exposed to humans depending on the number of humans present | [40]   | --- |
| $\beta S \left( H - S/q_s \right)$ | $1 - \exp\left(-\beta S \left(1 - S/(q_sH)\right)\right)$ | **Refuge effect on $H$.** Parameter $q$ represents the fraction of humans exposed to snakes depending on the number of snakes present. | [40] | 17062, 26.0 |
| --- | --- | --- | --- | --- |
| $\beta HS \cdot \left\{ \frac{S}{1-\varepsilon + \varepsilon S} \right\} \frac{H}{1-\varepsilon + \varepsilon H}$ | $1 - \exp\left( -\beta S \cdot \left( \frac{S}{H-\varepsilon H + \varepsilon HS} + \frac{1}{1-\varepsilon + \varepsilon H} \right) \right)$ | **Separate asymptotic** term on $H$ or $S$, where $0 \leq \varepsilon \leq 1$. When parameter $\varepsilon = 0$, the expression reduces to the simple mass action model, otherwise the effect of $H$ or $S$ becomes asymptotic. | [41] | --- |
| $\beta HS \cdot \left\{ \frac{1}{c + S} \right\} \frac{1}{c + H}$ | $1 - \exp\left( -\beta S \cdot \left( \frac{1}{cH + SH} + \frac{1}{cH + H^2} \right) \right)$ | **Asymptotic** on $H$ or $S$. Parameter $c$ represents the number of $S$ or $H$ at which 50% of the contacts occur. | [41] | --- |
The spatial version of the simple mass action model converged with 1M iterations, and had an even higher correlation with Ediriweera et al. [23]'s estimates, $r = 0.87$ (d. f. = 81, $P = 0$) for incidence and $r = 0.97$ (d. f. = 29, $P = 0$) for the number of bites (Figure 2).

The decomposition of contact rates that worked best was estimating a contact rate for each snake species and correcting snake abundance in relation to human population density by land cover class and log-transforming human population density:

$$\beta(H, L) = \exp(\beta_0(l) + \beta_1(l) \ln(H)^2) \quad 4.1$$

All the parameters of the spatial and non-spatial simple mass action model converged (Table 2) and did not exceed the very strict threshold of 1.05 of the Gelman test (very similar variances between and within chains; Supplementary materials, Table S1). The estimated effects of humans on snake abundance resulted in different responses of incidence rates to human population and snake abundance in each land cover class (Figure 3).
Table 2. Parameter estimates for the mass action models for snakebites. \( \beta_{i,l} \) parameters are those of the function of human population density to adjust total snake abundance in relation to humans in each land cover class. \( r_l \) are the negative binomial dispersion parameter for each land cover class. \( B_s \) are the estimated contact rates for each snake species after adjusting the point intensities for relative abundances and weighting for aggressiveness behaviour. The star * indicates the parameters whose 95% credible intervals do not contain zero (only relevant to \( \beta_{i,l} \)). Rows with grey background show estimates for the spatial version of the model.

| \( \theta \)         | Agriculture | Degraded | Forest   | Tea       | Urban         |
|---------------------|-------------|----------|----------|-----------|---------------|
| \( \beta_{0,l} \)   | -12.9 (0.19)* | -12.84 (0.2)* | -13.18 (0.21)* | -11.91 (0.26)* | -11.27 (0.61)* |
| \( \beta_{1,l} \)   | -12.9 (0.11)* | -12.87 (0.11)* | -13.11 (0.12)* | -11.84 (0.15)* | -11.32 (0.2)*   |
| \( r_l \)           | 23.70 (2.95) | 16.82 (1.13) | 9.32 (1.16)  | 7.18 (0.69)  | 12.10 (4.52)   |

| \( B_s \)            | \( B. caeruleus \) | \( B. ceylonicus \) | \( D. russelli \) | \( E. carinatus \) | \( H. spp \) | \( N. naja \) | \( T. trig. \) |
|----------------------|--------------------|--------------------|------------------|--------------------|-------------|--------------|-------------|
| \( 3.48 (0.56) \)    | 5.30 (2.85)        | 1.17 (0.37)        | 2.99 (1.07)      | 0.036 (0.02)       | 8.48 (1.29) | 0.17 (0.16) |
| \( 4.34 (0.48) \)    | 5.58 (2.26)        | 1.72 (0.39)        | 2.81 (0.97)      | 0.047 (0.015)      | 3.51 (0.69) | 0.14 (0.11) |

Model parameters

Parameters of the correction of snake abundance in relation to human population density (\( \beta_{0(l)} \) and \( \beta_{1(l)} \), equation 4.1) were all significantly negative (Table 2), indicating that humans tend to decrease snake abundance in all land cover classes. Also, given significant differences between land cover classes, the effect of humans on snakes depends on predominant land cover class. The largest effect was estimated for tea and urban cover (snakes decrease faster with human population density), intermediate in forest and degraded forest, and smallest in agriculture (snakes decrease the least with human population density, Table 2).
Regarding individual species’ contact rates, the Indian cobra (*Naja naja*) had the highest estimated rate, followed by the Ceylon krait (*Bungarus ceylonicus*) and the common krait (*B. caeruleus*). The lowest contact rate was estimated for the hump-nosed viper (*Hypnale spp*).

These contact rates showed no relationship with species’ relative abundances, indicating that factors not represented in the decomposed contact rates (i.e., frequency of venom injection, time of activity aligned with human activities) are critical but unobserved determinants of risk patterns. Note, that the estimated rates are not statements of how frequently humans encounter them. Estimated parameters should only be interpreted as indices of species’ importance for snakebites relative to their abundance and that of humans where they occur. Also, these parameters are negatively correlated with those estimated to adjust abundance in relation to humans. Every order of magnitude of increase in the size of the $B_s$ contact rates must be accompanied by an absolute decrease in log-scale of the value of $\beta_{0(i)}$ parameter of equation 4.1 (e.g. $B_s \times 10 \rightarrow \beta_{0(i)} - \ln(10)$, or $B_s / 10 \rightarrow \beta_{0(i)} + \ln(10)$), allowing the interpretations above for the individual species. The magnitude of these parameters indicates the average number of snakes in logarithmic scale that are lost for every human, resulting in faster declines in urban land cover, and slowest in agriculture (Table 2). The effect of both humans and snakes on snakebite incidence in each land cover class is represented visually in Figure 3.

**Envenoming model**

The fact that the random-intercept envenoming model (equation 3.2) was the more adequate, indicated that land cover influenced the probability that a snakebite resulted in envenoming. The correlation between envenoming incidence predicted by the spatial model and the data was $r = 0.85$ (d. f. = 23, $P = 0$; Figure 4, right panel) and for the number of envenoming cases was $r = 0.93$ (d.f. = 9, $P = 0$; Figure 4, top left panel). Convergence statistics for the spatial model are given in Supplementary materials Table S2 and Figure S4.
The snake species that had the largest significantly positive fitted effect on the probability of envenoming was *Bungarus caeruleus*, indicating that this species explains most of the spatial heterogeneity of the probability that bites result in envenoming in Sri Lanka (Table 3). *D. russelli* and *N. naja* also had significant effects in the outcome of snakebites but were significantly negative, indicating that risk of envenoming after a bite decreased with their predicted abundances (we address this counter-intuitive result in the Discussion). The remaining species' effects were not significantly different from zero, indicating that their contributions towards envenoming cannot be distinguished from random (Table 3).

**Table 3.** Parameter estimates of the model for probability of envenoming. *Intercept* are the estimated effects of each land cover, and *B*, are snake species' effects. The * symbol indicates that the 95% credible intervals of posterior samples do not contain zero. Rows with grey background show estimates for the spatial version of the model.

|       | **Agriculture** | **Degraded** | **Forest** | **Tea** | **Urban** |
|-------|-----------------|--------------|------------|---------|-----------|
| **Int** | 0.255 (0.07)*   | -0.394 (0.05)* | 0.056 (0.07) | -0.72 (0.04)* | 0.59 (0.17)* |
|        | -0.05 (0.04)    | -0.33 (0.03) * | -0.23 (0.05)* | -0.48 (0.03) * | 0.53 (0.11)* |
| **B**  | *B. caeruleus*  | *B. ceylonicus* | *D. russelli* | *E. carinatus* | *H. spp* | *N. naja* | *T. trig.* |
|        | 280.14 (13.99)* | -15.77 (32.12) | -97.34 (28.4)* | 5.49 (31.91) | -24.546 (23.74) | -290.34 (29.84)* | -2.88 (31.80) |
|        | 197.88 (13.41)* | -3.86 (31.68) | -165.129 (25.61)* | 5.22 (31.98) | -34.24 (19.77) | -373.43 (27.66)* | -1.64 (31.59) |
| **r** |                 |              |            |         | 18.59 (1.09) |
|       |                 |              |            |         | 49.69 (0.41) |

Land cover classes also had significant effects on the probability that snakebites resulted in
envenoming. *Agriculture*, had the largest significantly positive effect followed by *urban*.

*Degraded forest* had the largest significantly negative effect, followed by *tea*. The only land cover class with a non-significant effect was *forest*, which suggested that envenoming after a snakebite is more likely to be a function of the biting snake than of the environmental or social context of snake-bitten people in *forest* environments (Table 3, and see discussion on the role of land cover).

**Discussion**

Mathematical models have been critical tools for understanding and controlling the transmission of zoonotic diseases, but despite many ecological and epidemiological similarities few such models exist for snakebite (e.g. [9]). Here, we mapped snakebite and envenoming incidence using a mathematical model that represents human-snake interactions and their outcomes, adapting a mass action model usually applied to the transmission of infectious diseases [30]. We treated venom as pathogenic agent transmitted between venomous snakes and susceptible humans, and tested various functional relationships describing the human-snake contact process and its outcomes. Incidence rates were successfully mapped by estimating contact rates between all medically relevant snakes of Sri Lanka and humans, and by accounting for human and snake factors known to be important determinants of snakebite and envenoming incidence. Human factors included social, economic and cultural by categorising parameters by land cover, which serves as a powerful socio-economic proxy [29]. Snake factors included biological characteristics of the different species, like aggressiveness and severity of the envenoming illness. Furthermore, parameters in the model are sensitive to climate, land cover and topography via their effects on snake population estimates [28]. As such, we have developed a generalisable epidemiological model for snakebite that could be transferrable (given local data) to other time frames to forecast.
Predicting spatial and temporal patterns (including future changes) of snakebite risk is possible with purely statistical methods or by focusing only on one or two components of snakebite risk (e.g., [18,42]). An advantage of our approach, however, is that it is process-based and generalisable, explicitly capturing the relevant snakebite processes (e.g., human-snake contact patterns, biological traits of venomous species) to predict epidemiologically meaningful measures of snakebite risk. Such an approach may be more transferrable (i.e., when forecasting burden in other regions) and better suited to forecasting impacts of global change (e.g., including climate change, land-use change and socio-economic development), where a number of complex and potentially interactive mechanisms could push burden in different directions. However, the success of such applications still depends on the availability of relevant data to parameterise the model.

In particular, snake occurrence records and behavioural trait data were the raw material upon which we built our model [28]. Hence developing, improving and applying similar frameworks in other regions requires reliable occurrence data in relation to human population density as well as improved ecological information on venomous snakes [28,43], both of which can be regarded as high priorities for future work [44].

To the best of our knowledge, the only previous study of a mathematical model for snakebite comparable to ours, is Bravo-Vega et al. [9]. We considerably extend their approach by decomposing contact rates to incorporate both human and snake factors. The first snake aspect of the decomposed contact rate $\beta$ represents known (aggressiveness $-A_s$ and envenoming $-E_s$ indices) and unknown biological aspects (estimated statistically) of multiple species. The unknown estimated snake factors are likely related to the alignment of human-snake activity periods (Table 2 for snakebite model; [26]) and species' propensities to inject venom during a bite (Table 3 for envenoming model; [20,45]). Also, the estimated parameters summarise snake species' biologies and how these relate to human social, economic,
occupational and cultural aspects relevant for snakebite epidemiology. For instance, rice
paddy farmers are more susceptible to Russell’s viper bites (*Daboia russelii*) because rice is
usually harvested barefoot in Sri Lanka [46,47]; common krait (*Bungarus caeruleus*) bites
occur among the poorest of the poor while victims are asleep on the floor [46]; while *Hypnale*
spp. envenoming victims are mostly women who are traditionally in charge of home garden
maintenance where this species inhabits leaf litter [48]. These examples show how species’
effects on snakebite are intertwined with human socioeconomic and cultural factors.

The second aspect of the decomposed contact rate was the adjustment of snake abundance as
da function of land cover and human population density. Here, land cover may represent
predominant occupation and socioeconomic status [29], both of which are known to be
important snakebite risk factors [22]. Furthermore, we found that the probability that
snakebites result in envenoming (Table 3) is also significantly influenced by land cover,
especially in urban and agricultural areas. The latter is supported by empirical evidence, as
agricultural workers are at greatest risk of snakebite envenoming [22,49]. Consequently, the
estimated effects by land cover class summarise snake responses to humans, and effects of
human factors such as agricultural occupation and economic status on snakebite and
envenoming incidences.

In contrast with the conceptual and theoretical strengths of our approach, important
questions arise to address in future work, for instance: 1) should models be developed with
field data instead of estimates? 2) How does uncertainty and artefacts of incidence estimates
affect selection and estimates of our model? 3) Why do highly medically-important species’
decrease the probability that bites are envenoming? First question, we infer that a suitable
model for field-collected data may be simpler than ours, for which snake abundance estimates
in relation to humans should be more robust than currently available [28]. The second point is
likely to affect uncertainty of our results, but we interpret the very high similarity between
results as an indication of robustness because most data were independent, apart from
human population density, which we discussed above [23]. Finally the negative coefficients
estimated for D. russelii and N. naja (Table 3) indicate that the probability that a bite results
in envenoming decreases when these species are more abundant. Such a negative relationship
is unexpected as both are considered among the primary cause of snakebites in Sri Lanka
[50]. However, these contradictory estimates may result from the east vs west difference in
envenoming incidence in Sri Lanka (Figure 4). Envenoming burden is much higher in eastern
than western Sri Lanka, but both species are nearly equally abundant on either side [28].
Hence their abundances cannot explain the east vs west spatial heterogeneity of
envenomings, making estimation of their effects difficult with the methods used here.
Alternatively, the estimated negative effects for these species could arise if the predicted
abundances of N. naja and D. russelii actually serve as proxies for the abundances of non-
envenoming species. Abundance surrogacy is relatively common among habitat generalists
[51] and non-envenoming snakes are commonly involved in snakebite cases [52], resulting in
decreasing risk with the abundance of those non-medically relevant species.
With careful consideration of the strengths and weaknesses of our approach, we encourage
applying and testing our framework in data poor geographical areas for predicting risk in the
absence of other data (e.g., national community survey data) or for testing mitigation
interventions. Doing so, however, does require some baseline data as inputs. As mentioned
above, the first requirement is a collection of geographical occurrence data of venomous
snakes to estimate abundance patterns. Methods and concepts for the analysis of this kind of
data in relation to the environment are well established and are described elsewhere (e.g.
[53]), and here we used point process models (PPMs) for this purpose given important
limitations noted for other common distribution modelling methods (e.g., Maxent) [28,54].
Second is to include some key snake biological/behavioural characteristics for the
decomposed contact rates. Relevant traits include aggressiveness, overlap of activity periods
with humans [26], venom toxicity to humans and propensity to inject venom after a bite [20].

Lastly, socioeconomic and demographic data may also be used if associated risk factors are well known in the study region. Predictions obtained with the suggested approach will not necessarily represent incidence rates or another measure of burden, but are likely to be broadly correlated with them [28].

Achieving the burden reduction goals laid out in the snakebite roadmap (reducing burden by 50% by 2050; [11]) is an exceptionally ambitious target, requiring advances to our basic understanding of snakebite epidemiology and its treatment. As for other zoonotic diseases, global changes are likely already influencing snakebite and envenoming dynamics, and efficient management will need to accommodate for such changes. However, unlike for many zoonoses, few tools currently exist for snakebite that both shed light on its mechanistic underpinnings and provide avenues for burden mapping and prediction under scenarios of global change or for testing interventions. Reframing snakebite as a zoonotic disease has considerably improved our understanding of its epidemiology: it is a dynamic process, its burden is the result of the effects of humans on the abundance of snakes and both affect the burden of snakebite envenoming. The ecological footprint of humans, via land use, represents key characteristics of local populations that are related to snakebite levels. All these factors, and the nature of snake models used, make our model a simple, yet effective tool to forecast the impacts of global environmental change on snakebite burden. Such exercises are necessary to develop relevant interventions for the present and into the future to solve the snakebite crisis.

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Conflict of interest

Authors have no competing financial interests or of any other nature to disclose.

Data availability

Data and code are currently hosted in the repository

https://github.com/gerardommc/Snakebite-zoonotic-transmission and will be archived in Zenodo upon publication.

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Figure 1

Number of snake species and their geographic distributions and population densities

Species' propensity to bite, and inject venom with a composition and dose that cause various envenoming diseases.

Alignment between human settlements and venomous snake populations

Individual-level factors that influence likelihood of encounter with types of snakes and their outcomes

Risk factors - socioeconomic, cultural, occupational and gender

Snakebite burden

Snake diversity, distribution and abundance

Aggressiveness, venom injection and toxicity

Human population density

Effects of humans on snake distribution and abundance

\[ F(H, S, \theta) \]
Figure 2

Snakebite incidence

Random effects

RMSE

Number of snakebites

Estimates residuals

Survey data residuals

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Figure 3
Figure 4