Appendix

Mortality methods

GBD 2019 venomous animal contact estimation

The GBD study methods and results have been described in extensive detail elsewhere including description of the analytical estimation framework used to measure deaths, YLLs, incidence, prevalence, YLDs, and disability-adjusted life years (DALYs).[1,2] We used the GBD 2019 estimates for overall venomous animal contact as a platform for our analysis, focusing only on the cause-specific mortality component. A summary of the GBD 2019 estimation approach for mortality from venomous animal contact is as follows.

The case definition for a venomous animal contact death in GBD 2019 was "death resulting from unintentionally being bitten by, stung by, or exposed to a non-human venomous animal". We used ICD-9 codes E905-E905.99 and ICD-10 codes X20-X29.9 to identify deaths that met this case definition in vital registration (VR) data. We additionally identified verbal autopsy (VA) data to supplement VR data. Once data from all available sources were identified, the datasets were then cleaned and mapped to the GBD cause list using the GBD 2019 cause hierarchy.

Next, ensemble models were conducted using the GBD cause of death ensemble modelling (CODEm) method for estimating venomous animal contact mortality by age, sex, location, and year. CODEm is described in more detail elsewhere but essentially explores a large variety of possible models to estimate trends in causes of death using an algorithm to select varying combinations of covariates that are run through several modelling classes.[3] Covariates are also included to guide predictions where data are sparse or absent. Covariates for venomous animal contact are listed in Appendix Table 1. An ensemble of best-performing models is created based on out-of-sample validity testing. Years of life lost (YLLs) are calculated by multiplying cause-specific mortality rates by the residual life expectancy at the age of death (supplementary appendix Table 2). These steps resulted in cause-specific mortality estimates for venomous animal contact, as reported in GBD 2019 capstone publications.

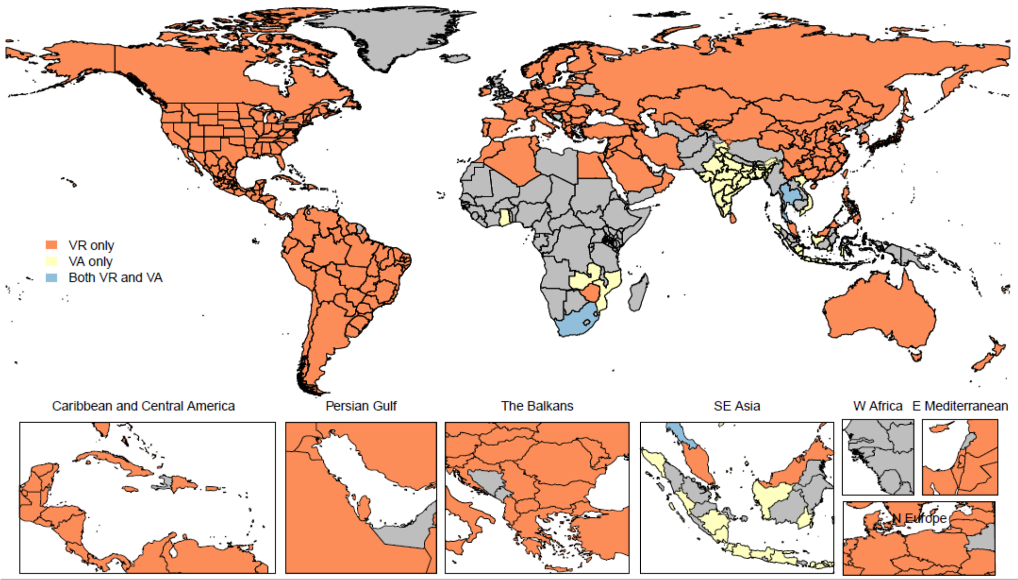
Covariate	GBD 2019 direction	Species-specific direction
Healthcare Access and Quality Index	-1	-1
Rainfall population-weighted (mm/yr)	1	0
Urbanicity	-1	-1
Proportion of population involved in agricultural activities	1	1
Population-weighted mean temperature	1	0
Socio-demographic Index	-1	-1
Absolute value of average latitude	-1	0
Education (years per capita)	-1	-1
Elevation over 1500m (proportion)	-1	0
Elevation under 100m (proportion)	-1	0
Log-transformed age-standardised SEV scalar: venom	1	1
Population density (over 1000 ppl/km^2, proportion)	-1	-1
Population density (under 150 ppl/km^2, proportion)	1	1
LDI (I$ per capita)	-1	-1
Proportion of population vulnerable to venomous snakebites[a]	1	1
Mean number of venomous snake species[a]	1	1

Appendix Table 1. Covariates and prior beta-coefficient directions used in the GBD 2019 venomous animal contact CODEm model and species-specific model. a: covariates extracted from Longbottom et al.'s manuscript on snakebite vulnerability.[4]

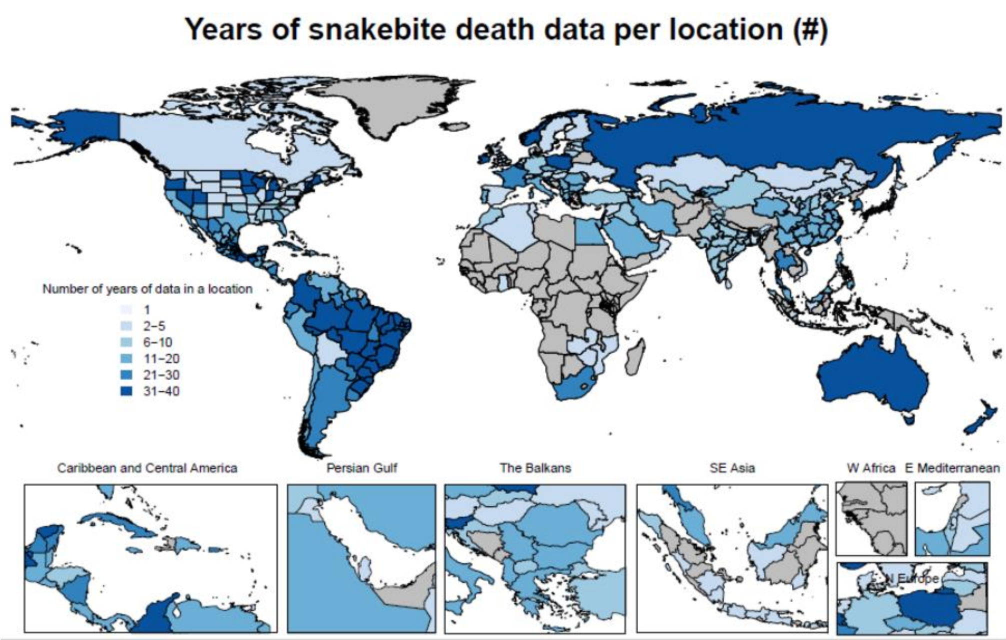
Snakebite-specific study design and data sources

After GBD 2019 venomous animal contact mortality was estimated, we undertook the following steps to estimate snakebite-specific mortality.

First, we reviewed all cause of death data that could be mapped directly to snakebites and the other species-specific categories. We also identified non-VR sources of data that could be used for snakebite deaths. Supplementary appendix Figure 1 shows locations that contain VR data, VA data, or both. The snakebite-specific model had 10 636 location-years of data. Geographic coverage is shown in Appendix Figures 1 and 2.



Appendix Figure 1. Map of Vital registration, verbal autopsy data coverage.

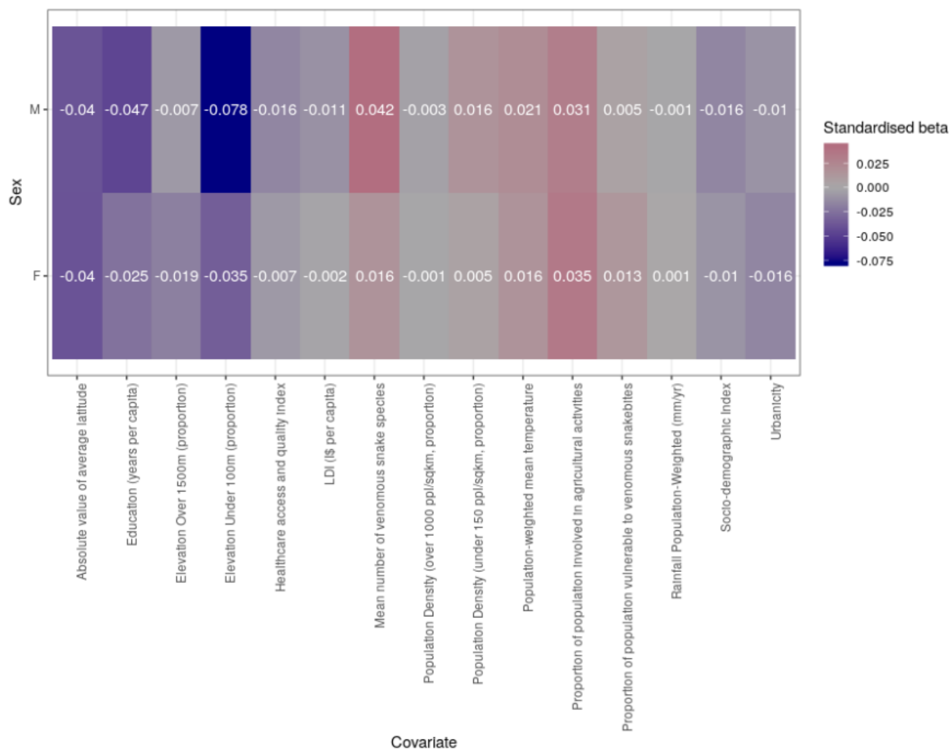


Appendix Figure 2. Map of input data and volume of location-years used in snakebite ST-GPR mortality modeling

After obtaining data, we applied a noise reduction processing step to the raw species-specific data. Noise reduction processing is based on a Poisson regression model and Bayesian averaging process that reduces stochastic variation. This process is essential to cause of death data processing in the GBD study and was adapted for our data. We also applied a process to redistribute ill-defined causes of death to the species-specific data. This process is also used in GBD cause of death data processing and is described in more detail in related literature.[2]

Snakebite-specific statistical analysis

Following noise reduction and redistribution of ill-defined causes of death, we developed statistical models based on the spatial-temporal Gaussian process regression (ST-GPR) modeling framework used elsewhere in GBD.[5] ST-GPR starts by fitting a mixed-effects linear prior and then fitting a second model based on the weighted residuals between the input data and the linear prior to make predictions for countries and years without data. Every combination of covariates (Appendix Table 1) was tested in a mixed-effects model with snakebite deaths per 100 000 people as the outcome variable. After testing candidate covariates, an ensemble of the best performing models was developed which acted as the first-stage linear prior in the ST-GPR model, weighted by out-of-sample root mean square error (RMSE). Covariate coefficients are shown in Appendix Figure 3.



Appendix Figure 3. Standardized beta coefficients of the 16 covariates used in the ensemble modeling approach. Standardized coefficients are equal to the beta coefficient per unit of the variable times the standard devition of the covariates over the standard deviation of the input data:

ST-GPR Parameters

Spaciotemporal Gaussian Process Regression (ST-GPR) has three different hyperparameters that are set to control the amount of temporal, age, and spatial smoothing. Time smoothing follows Equation 1, where j is the observed data point and I is the country-year-age-sex to be predicted. We set λ to be equal to 0.1, causing a high amount of smoothing over time due to a prior expectation that the burden of snakebite would not have significant change year to year.

$$Eq. 1: \ w_t = e^{-\lambda|time_i - time_j|}$$

Age weighting follows equation 2, where j is an observed data point, I is a country-year-age-sex point to be predicted, and ω is the set hyperparameter. We set omega to be 0.5, establishing a medium rate of smoothing over age to allow some effect while also giving ST-GPR the flexibility to follow data points closely.

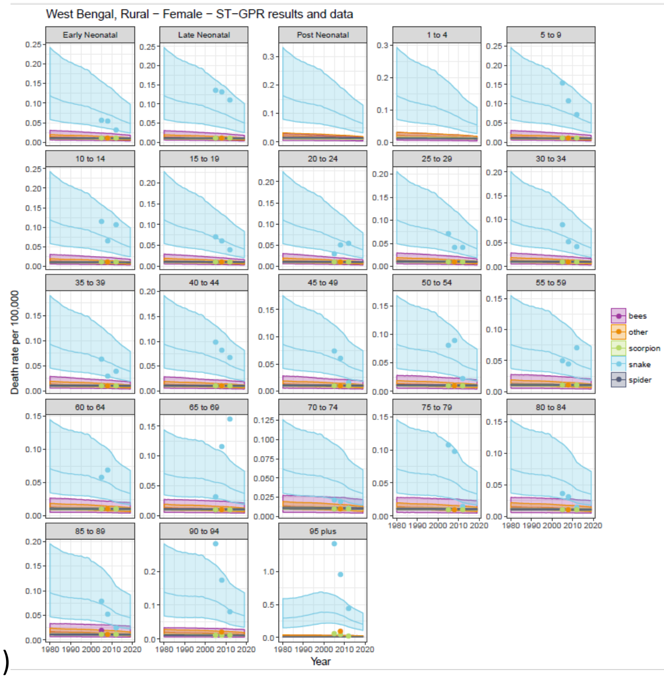
$$Eq. 2: age\ weight_{i,j} = \frac{1}{e^{\omega *|\ agegroup_i - agegroup_j\ |}}$$

Space weighting follows Eq. 3 below. We set zeta equal to 0.01, creating very little smoothing between countries and subnational locations. We believed there would be significant variation between countries due to ecology, health system strength, and other characteristics, and we allowed ST-GPR to follow the trends in a given location when provided with data to do so.

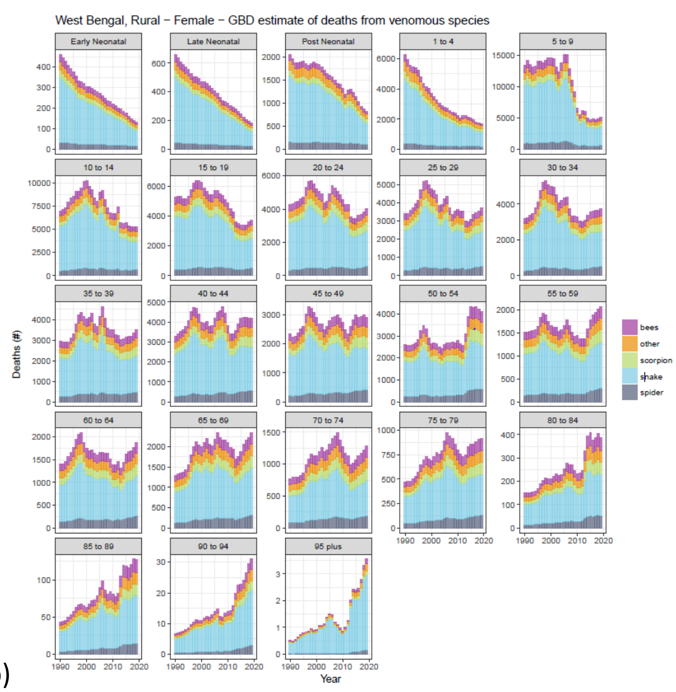
$$space\ weight = \begin{cases} \zeta^0 = 1 & for\ residuals\ within\ country\ i \\ \zeta^1 & for\ residuals\ within\ region\ j\ but\ not\ country\ i \\ \zeta^2 & for\ residuals\ not\ in\ region\ j \end{cases}$$

We ran ST-GPR models for snakes, bees, scorpions, spiders, and the fifth "other venom" category to estimate the rate of death from all five species for 205 countries, 22 age groups, males and females, for every year between 1980 and 2019 inclusive. For each of these results, we aggregated together the five different species to derive the proportion of overall venomous animal deaths due to snakebites. This proportion was applied to the GBD 2019 venomous animal contact results from 1990 to 2019 to calculate the snakebite cause-specific mortality rate (CSMR). Figure 2a displays the GBD 2019 all ages rate of death from venomous animal contact, while Figure 2b displays the proportion of those deaths due to just snakebite. Appendix Figure 3 shows example an example of the model fit and how they are applied to GBD 2019 results.

Results of proportional mortality within the venomous animal contact cause and age-standardized mortality per 100,000 in 2019 across both sexes is shown in Appendix Figure 4.

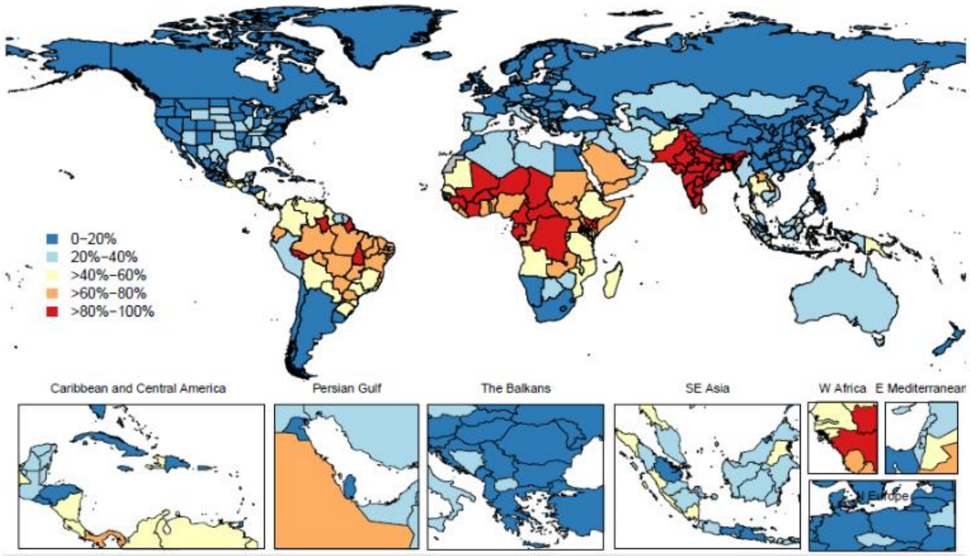


a)



b)

Appendix Figure 4. a) ST-GPR model results and inputs overlaid for the five different venomous species. b) proportions after aggregating model results from Figure 3a, applied to GBD 2019 venomous animal contact estimates.

a) 

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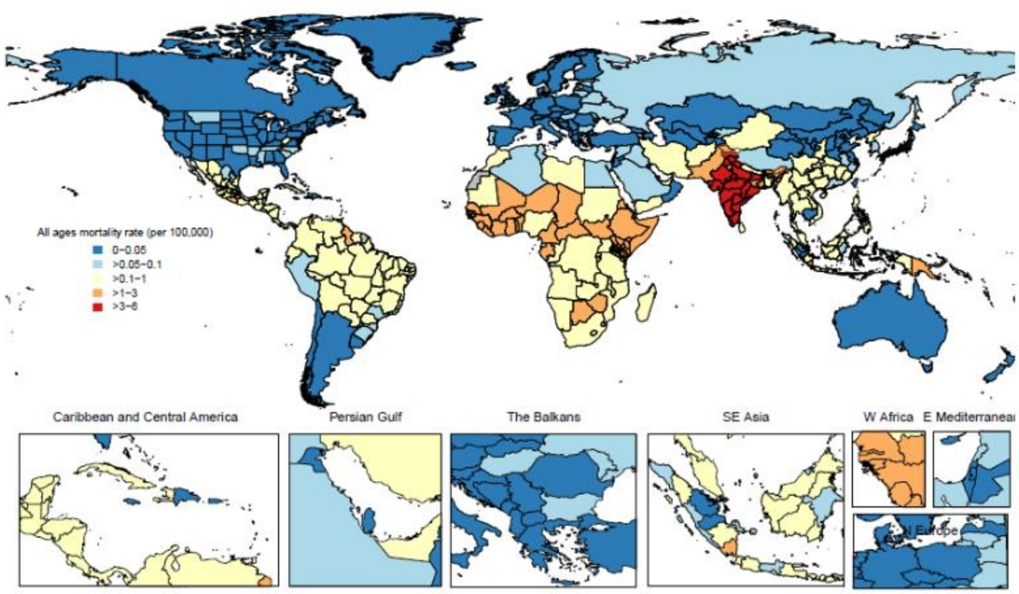


Appendix Figure 5. a) Proportion of all venomous animal contact deaths due just to snakes and b) age-standardized rate of deaths per 100,000 in 2019, both sexes.

Appendix Table 2. Epidemiological literature on snakebites used to estimate case fatality rates, age and sex distribution, and rates of nonfatal outcomes.

Study	Location	Neurotoxic CFR	Hemotoxic CFR	Incidence by 10-year age groups	Incidence by sex	Hemotoxic outcome information	Neurotoxic outcome information
A hospital based epidemiological study of snakebite in Paschim Medinipur district, West Bengal, India[6]	West Bengal	No	No	Yes	Yes	No	No
A hospital based epidemiological study of snakebite in Western Development Region, Nepal[7]	Nepal	No	No	Yes	Yes	No	No
A retrospective analysis of snake envenomation in the intensive care unit of a tertiary care hospital in Delhi[8]	Delhi	Yes	No	No	Yes	No	Yes
A retrospective review of snake bite victims admitted in a tertiary level teaching institute[9]	Andhra Pradesh	No	No	Yes	Yes	No	No
A retrospective study of snake bite envenomation in a tertiary care teaching hospital in Southern India[10]	Tamil Nadu	No	No	No	Yes	Yes	Yes
A retrospective study of use of polyvalent anti-snake venom and risk factors for mortality from snake bite in a tertiary care setting[11]	Maharashtra	Yes	Yes	No	Yes	No	No
A season of snakebite envenomation: presentation patterns, timing of care, anti-venom use, and case fatality rates from a hospital of southcentral Nepal[12]	Nepal	Yes	No	Yes	Yes	No	No
A Study of Clinical Profile of Snake Bite at a Tertiary Care Centre[13]	Maharashtra	Yes	Yes	No	Yes	Yes	Yes
A Study on the Clinico-Epidemiological Profile and the Outcome of Snake Bite Victims in a Tertiary Care Centre in Southern India[14]	Karnataka	Yes	Yes	No	Yes	Yes	Yes
Acute renal failure in snake envenomation: a large prospective study[15]	Tamil Nadu	No	No	No	Yes	Yes	No
Clinical and epidemiologic profile and predictors of outcome of poisonous snake bites - an analysis of 1,500 cases from a tertiary care center in Malabar, North Kerala, India[16]	Kerala	Yes	Yes	No	Yes	Yes	Yes
Clinical and investigative profile of patients having snakebite with special reference to acute kidney injury[17]	Gujarat	No	No	No	Yes	No	No
Clinical Profile and Outcome of Envenomous Snake-Bite At Tertiary Care Centre In Nellore- A Retrospective Study[18]	Andhra Pradesh	Yes	yes	No	Yes	Yes	Yes
Clinical profile of snake bite cases in Marathwada, India[19]	Maharashtra	Yes	Yes	Yes	Yes	No	No

Clinical profile of snake bite in a tertiary care hospital in South India[20]	Karnataka	No	No	No	Yes	Yes	Yes
Clinical profile, species-specific severity grading, and outcome determinants of snake envenomation: An Indian tertiary care hospital-based prospective study[21]	Karnataka	Yes	Yes	No	Yes	Yes	Yes
Clinico-epidemiological features of viper bite envenomation: a study from Manipal, South India[22]	Karnataka	No	Yes	No	No	Yes	No
Clinico-epidemiological Profile of Snake Bites over 6-year Period from a Rural Secondary Care Centre of Northern India: A Descriptive Study[23]	Jharkhand	No	No	No	Yes	Yes	Yes
Clinico-Epidemiological Profile of Snakebite Cases Admitted in a Tertiary Care Centre in South India: A 5 Years Study[24]	Karnataka	No	No	Yes	Yes	No	No
Demographic, epidemiologic and clinical profile of snake bite cases, presented to Emergency Medicine department, Ahmedabad, Gujarat[25]	Gujarat	No	No	No	Yes	No	No
Distinctive epidemiologic and clinical features of common krait (Bungarus caeruleus) bites in Sri Lanka.[26]	Sri Lanka	Yes	No	Yes	Yes	No	Yes
Envenoming by the Common Krait (Bungarus caeruleus) and Asian Cobra (Naja naja): Clinical Manifestations and Their Management in a Rural Setting[27]	Maharashtra	Yes	No	Yes	Yes	No	Yes
Epidemiological profile of snake bite at tertiary care hospital, North India[28]	Uttar Pradesh	No	No	No	Yes	No	No
Epidemiology and clinical picture of the Russell's viper (Daboia russelii russelii) bite in Anuradhapura, Sri Lanka: a prospective study of 336 patients.[29]	Sri Lanka	No	Yes	No	Yes	Yes	No
Epidemiology of snakebites based on field survey in Chitwan and Nawalparasi districts, Nepal[30]	Nepal	No	No	Yes	Yes	No	No
Epidemiology, clinical profile and management is sues of cobra (Naja naja) bites in Sri Lanka: first a uthenticated case series.[31]	Sri Lanka	Yes	No	No	Yes	No	Yes
Exploring circulatory shock and mortality in viper envenomation: A prospective observational study from India[32]	Puducherry	No	Yes	No	Yes	Yes	No
Incidence & management practices of snakebite: A retrospective study at Sub-District Hospital, Dahanu, Maharashtra, India[33]	Maharashtra	No	No	No	Yes	No	No
Incidence and treatment of snakebites in West Bengal, India[34]	West Bengal	No	No	No	Yes	Yes	Yes
Management of snake-bite in rural Maharashtra: a 10-year experience[35]	Maharashtra	Yes	Yes	Yes	Yes	Yes	Yes

Mass awareness regarding snake bite induced early morning neuroparalysis can prevent many deaths in North India[36]	Himachal Pradesh	No	No	No	Yes	No	No
Neurotoxicity in Russell's viper (Daboia russelii) envenoming in Sri Lanka: a clinical and neurophysiological study.[37]	Sri Lanka	No	No	No	Yes	Yes	No
Outcome determinants of snakebites in North Bihar, India: a prospective hospital based study[38]	Bihar	No	No	No	Yes	No	No
Predictors of mortality in patients of poisonous snake bite: Experience from a tertiary care hospital in Central India[39]	Maharashtra	Yes	Yes	No	Yes	No	No
Predictors of mortality in vasculotoxic and neurotoxic snakebite patients in a tertiary care institute in Jharkhand, India[40]	Jharkhand	No	No	No	No	Yes	Yes
Profile of snakebite envenoming in rural Maharashtra, India[41]	Maharashtra	Yes	Yes	Yes	Yes	Yes	Yes
Retrospective study of neuroparalytic snake envenomation in a tertiary care hospital of Chhattisgarh[42]	Chhattisgarh	Yes	No	No	Yes	No	Yes
Snake envenomation in a north Indian hospital[43]	Punjab	No	No	No	Yes	Yes	Yes
Snake venom poisoning: Experience with 633 cases[44]	Karnataka	No	No	No	Yes	No	No
Snakebite and Its Socio-Economic Impact on the Rural Population of Tamil Nadu, India[45]	Tamil Nadu	No	No	Yes	Yes	No	No
Snakebite envenoming in Kerala, South India: clinical profile and factors involved in adverse outcomes[46]	Kerala	No	No	No	Yes	Yes	No
Snakebite profile from a medical college in rural setting in the hills of Himachal Pradesh, India[47]	Himachal Pradesh	No	No	No	Yes	No	No
Snakebite: Admissions at a tertiary health centre in Maharashtra, India[48]	Maharashtra	Yes	Yes	No	No	No	No
Study of clinical and epidemiological profile of poisonous snake bite in a tertiary centre in North Kerala[49]	Kerala	No	Yes	No	Yes	Yes	No
Study of snake bite cases admitted in tertiary care hospital in Nagpur[50]	Maharashtra	No	No	No	Yes	Yes	Yes
Use of Molecular Diagnostic Tools for the Identification of Species Responsible for Snakebite in Nepal: A Pilot Study[51]	Nepal	Yes	No	No	Yes	Yes	Yes

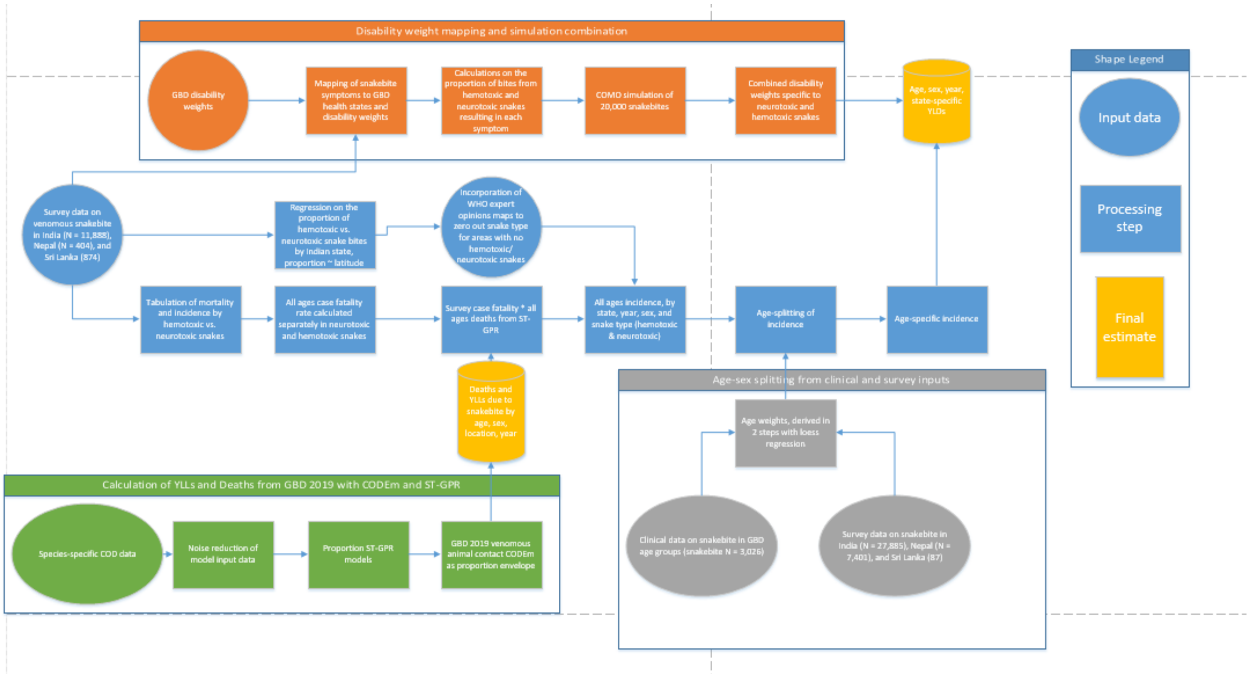
Nonfatal supplementary information

Literature review

Source metadata is included above in Appendix Table 2.

Methods

Flow chart



Appendix Figure 6. Flow chart of methods used in estimation of snakebite burden

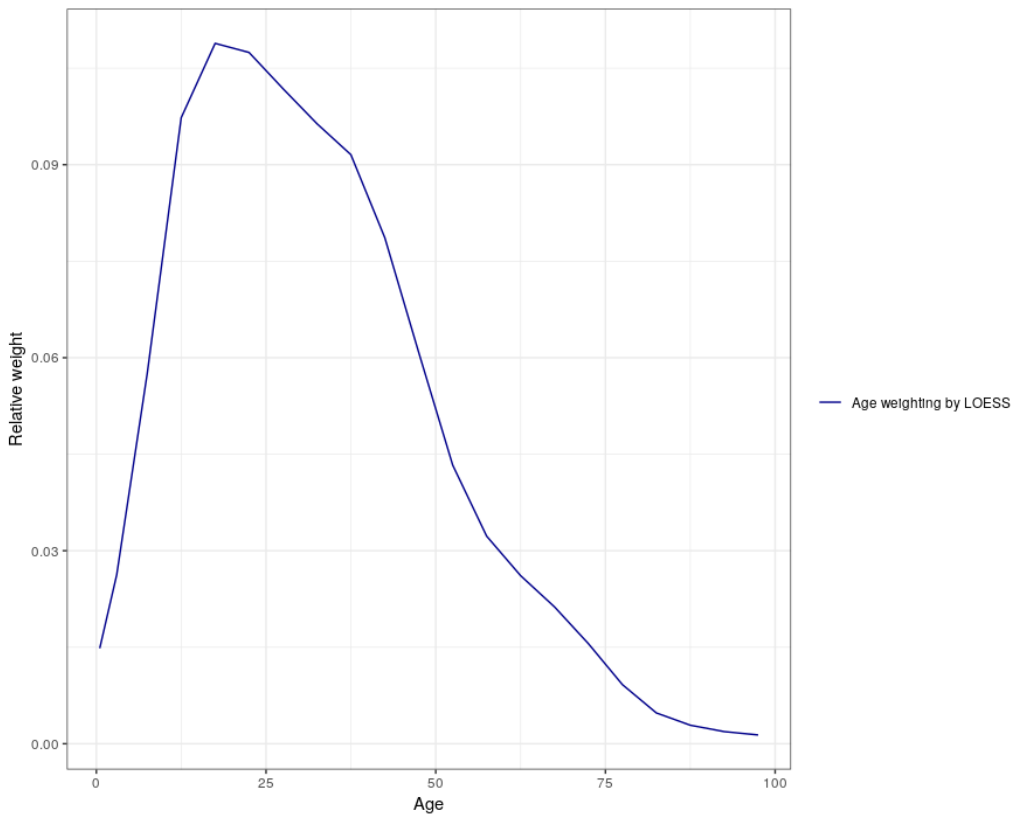
Age- and sex-splitting of incidence data

The GBD produces all estimates in 5-year age windows, while the most detailed studies above provided age patterns in 10-year age windows. To split these 10-year age windows, inpatient hospital data from the state of Karnataka that had admissions by age, sex, and ICD10 was used.[52] The data was queried for the ICD10 codes T63* and X2*, where star represents any code beyond the first digits. Because this data came exclusively from inpatient hospital admissions, the data was scaled by the GBD estimates of the number of inpatient admissions per capita from Karnataka (Appendix Table 3). This step was needed because weights were meant to calculate the incidence of snakebites across the population, which has a different age structure than the age structure of the inpatient population. See appendix Table XX for the inpatient admission per capita rate applied to the data.

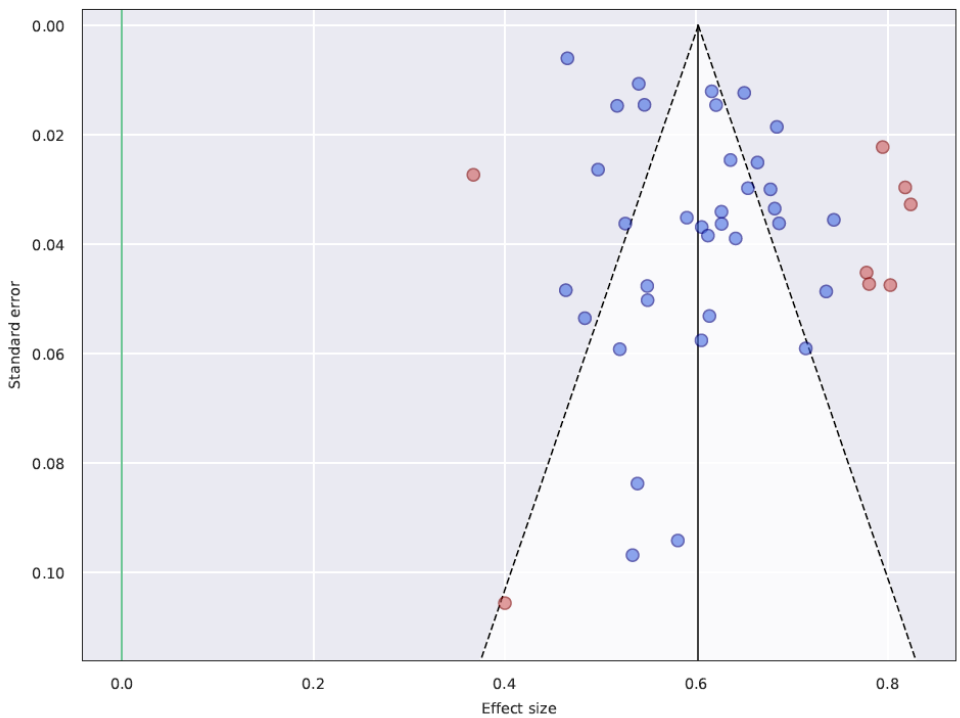
To split incidence over all ages to age- and sex-specific values, the distribution of bites over age was estimated from clinical and literature data. Age weights were calculated in two stages. First, the distribution of venomous snakebites over age in clinical data that had been adjusted for the inpatient utilization rate was calculated. The relative age weight was equal to the number of bites that occurred in a specific age, divided by the total number of bites that occurred across all ages. Five-year age weights were smoothed using a LOESS regression.

These clinically derived five-year age weights were then applied to the 10-year age groups between 0 and 60 years old, and included 35,580 incidence cases across 9 studies. After splitting each survey's 10-year age group into the correct GBD age groups, the surveys were re-aggregated to estimate a new set of weights for 5-year age groups, which were also smoothed using a LOESS regression over age. From age 60 and older, weights from the clinical source alone were used, because few surveys included detailed incidence information above age 60. Appendix Figure 7 shows the age weight distribution.

The proportion of bites due to males or females was derived through MR-BRT with inputs from 43 studies and 22,671 bites. A funnel plot depicting the model inputs and estimate are shown in Appendix Figure 8. The MR-BRT model estimate was that 60.2% (47.2 to 73.5) of bites occurred in males.



Appendix Figure 7. Relative age weights extracted from clinical and literature sources and modeled using LOESS. Across all ages, the total weight sums to one, and these weights were used to distribute incidence over all ages to age-specific incidence.



Appendix Figure 8. Funnel plot showing the sex-ratio of bites, modeled in MR-BRT. Effect size is equal to bites due to males over bites due to both sexes. Red points indicate input data points that were identified as outliers by MR-BRT's likelihood estimator, and removed from the modeling process. The vertical line represents the mean estimate of the model.

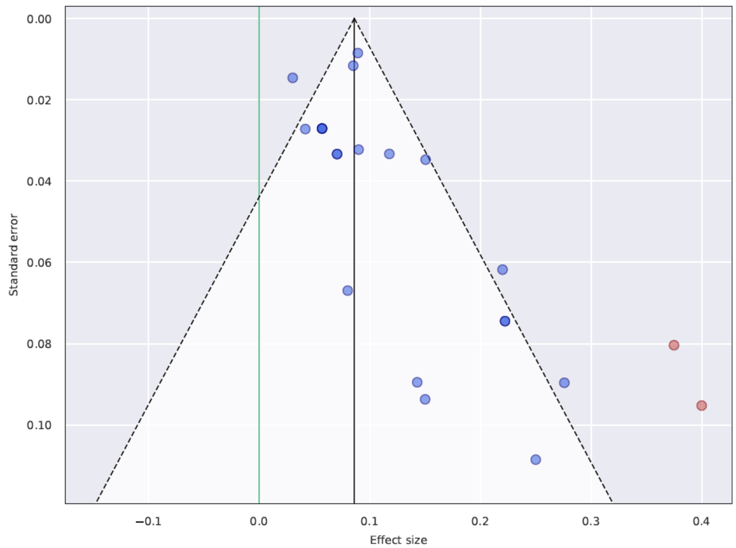
Appendix Table 3. Estimates from the GBD of the annual inpatient admissions per capita in 2015 for Karnataka, the state of India where the inpatient data source hospital is located.

Age group	Sex	Inpatient admissions per capita
<1 year	Male	0.031705384
<1 year	Female	0.0377282
1 to 4	Male	0.01237598
1 to 4	Female	0.013917278
10 to 14	Male	0.00770557
10 to 14	Female	0.008334483
12 to 23 months	Male	0.013067071
12 to 23 months	Female	0.016573933
15 to 19	Male	0.010434222
15 to 19	Female	0.012808817
2 to 4	Male	0.012146823
2 to 4	Female	0.013044733
20 to 24	Male	0.012480772
20 to 24	Female	0.022195524
25 to 29	Male	0.013224362
25 to 29	Female	0.025329079
30 to 34	Male	0.011181725
30 to 34	Female	0.020912707
35 to 39	Male	0.013302509
35 to 39	Female	0.01664488
40 to 44	Male	0.015636304
40 to 44	Female	0.013392635
45 to 49	Male	0.019646096
45 to 49	Female	0.012013732
5 to 9	Male	0.00879586
5 to 9	Female	0.008722381
50 to 54	Male	0.020901055
50 to 54	Female	0.013622305
55 to 59	Male	0.01563069
55 to 59	Female	0.016474822
60 to 64	Male	0.017987385
60 to 64	Female	0.025203155
65 to 69	Male	0.023976715
65 to 69	Female	0.034272213
70 to 74	Male	0.025299639
70 to 74	Female	0.04657559
75 to 79	Male	0.031840117
75 to 79	Female	0.055625443
80 to 84	Male	0.033142572
80 to 84	Female	0.073846144
85 to 89	Male	0.036227498
85 to 89	Female	0.08279328
90 to 94	Male	0.03954175
90 to 94	Female	0.09088337
95 plus	Male	0.043894839
95 plus	Female	0.098730566

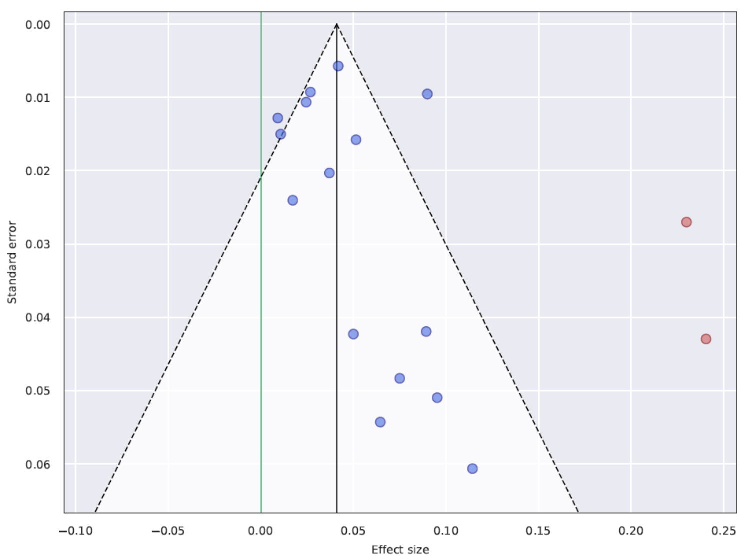
MR-BRT models of CFR and short-term health outcomes

Case-fatality rate from neurotoxic and hemotoxic snakes were modeled using MR-BRT. Trimming was set to 10% of data (Appendix Figure 9). MR-BRT models were also run for the short-term health outcomes of neurotoxic and hemotoxic snakes, and the funnel plots are shown in Appendix Figure 10.

a) Neurotoxic CFR MR-BRT model

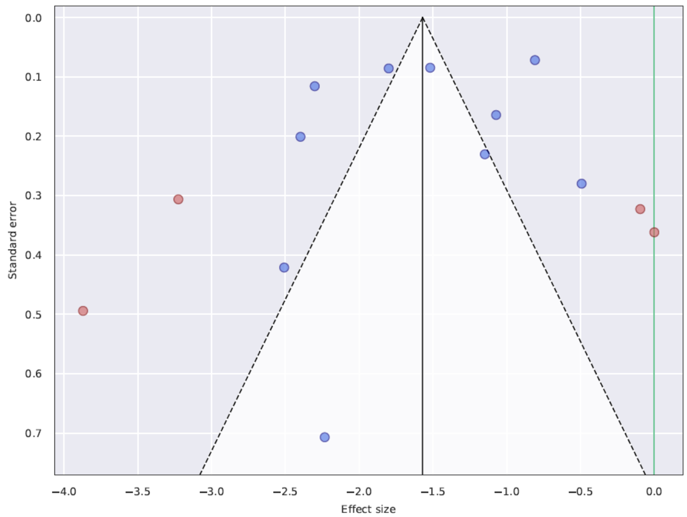


b) Hemotoxic CFR model

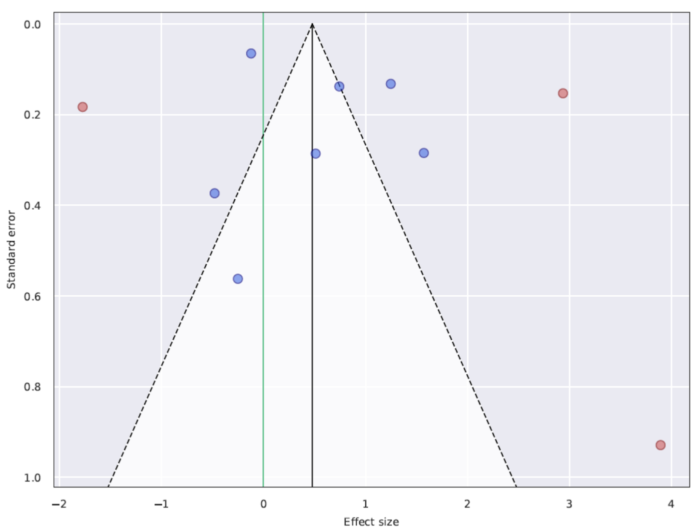


Appendix Figure 9. MR-BRT models of the case-fatality rate from a) hemotoxic and b) neurotoxic snakes. Data points represent proportions extracted from epidemiological studies. Red points represent inputs that were determined to be outliers by the MR-BRT likelihood estimator. The vertical line represents the mean estimate of the MR-BRT model.

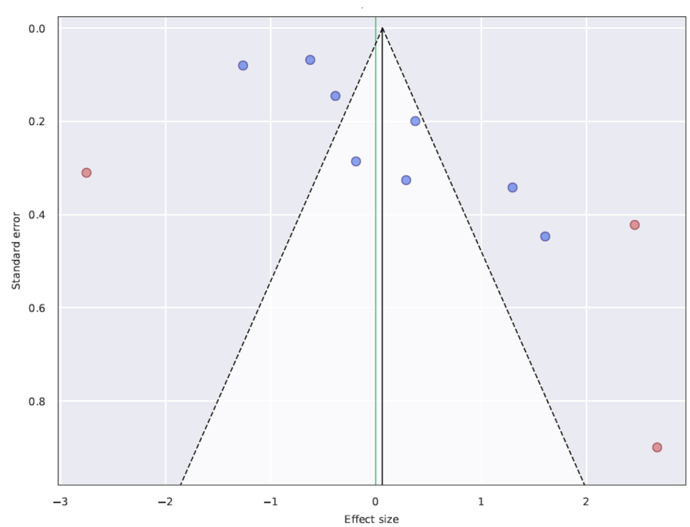
A) Hemotoxic – Acute kidney failure



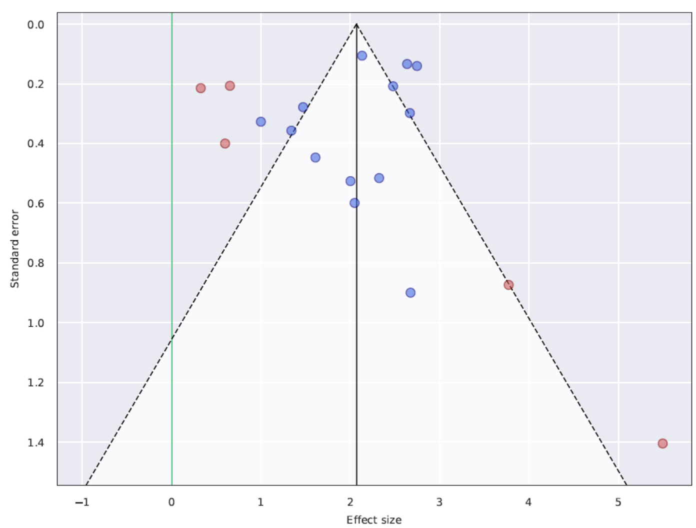
B) Hemotoxic – Coagulopathy:



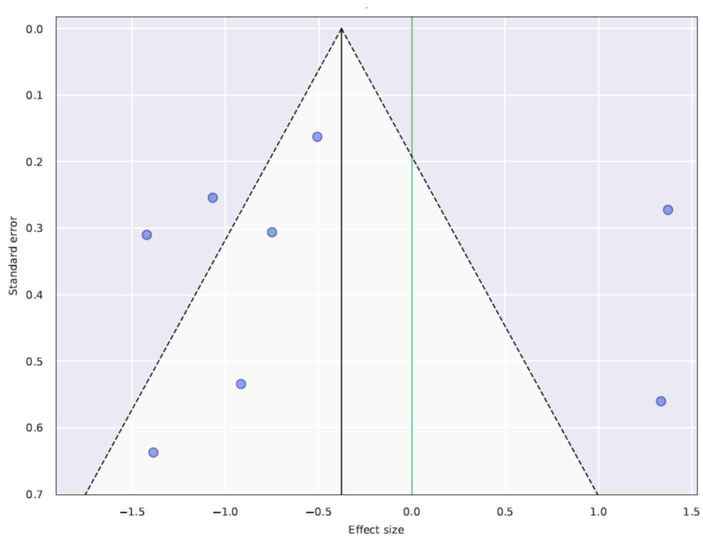
C) Hemotoxic – Local skin blister and infection:



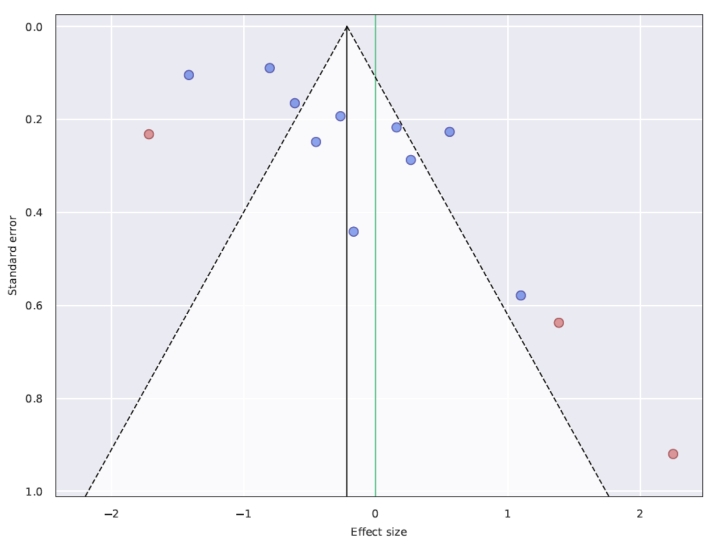
D) Hemotoxic – Open wound, including pain and swelling



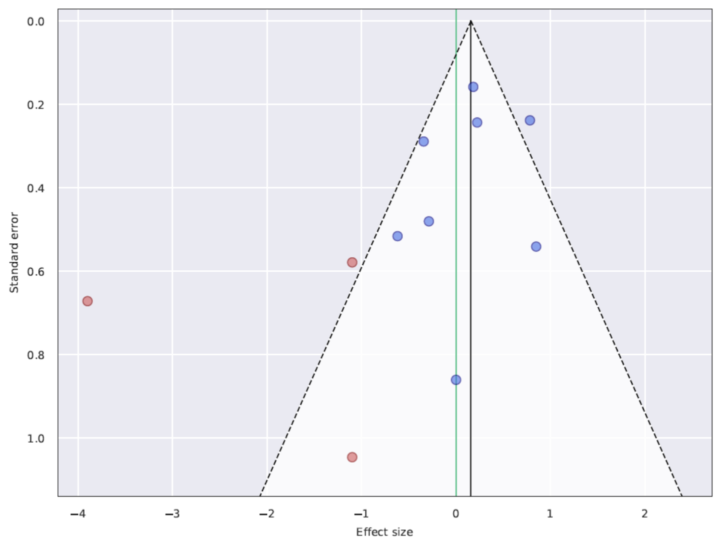
E) Neurotoxic – Paralysis



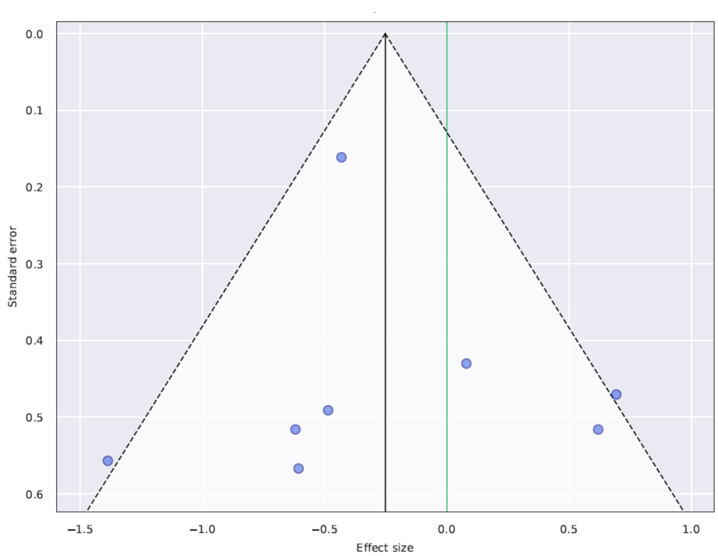
F) Neurotoxic – Respiratory failure



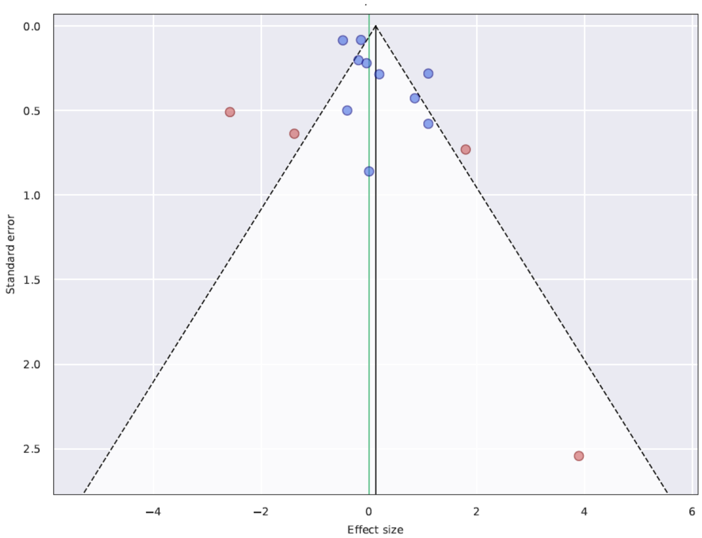
G) Neurotoxic – Neurological weakness



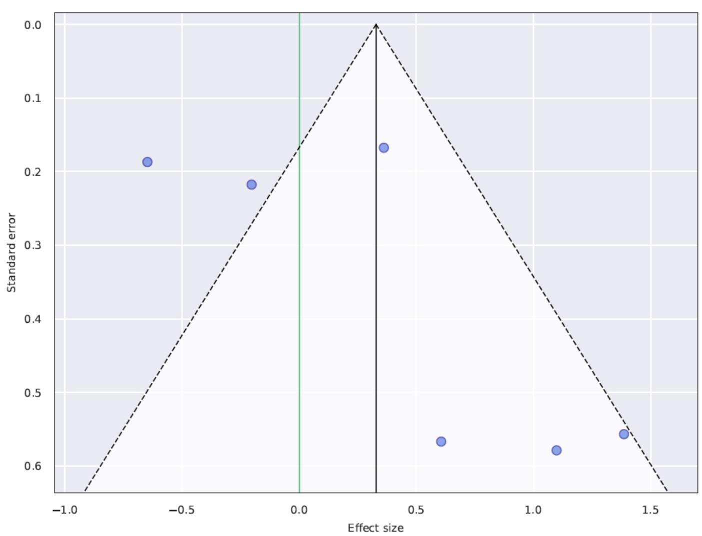
H) Neurotoxic – Local skin blister and infection



I) Neurotoxic – Double and blurry vision



J) Neurotoxic – Open wound, including pain and swelling



Appendix Figure 10. Funnel plots of the MR-BRT models of incidence of short-term health outcomes. Data points represent proportions extracted from literature surveys. Red points represent inputs that were determined to be outliers by the MR-BRT likelihood estimator. Models were conducted of the logit of the proportion. The vertical line represents the mean estimate of the MR-BRT model.

Long-term mapping and disability

Appendix Table 5. Long-term health outcome mapping including their incidence and disability weight

Snake type	Short term sequela	Long term sequela	Disability weight (95% UI)	Duration	Proportion of short-term bites resulting in long-term complications
Hemotoxic	Acute kidney failure	Stage 4 chronic kidney disease	0.104 (0.07-0.147)	lifetime	0.15
Hemotoxic	Acute kidney failure	Hypopituitarism	0.288 (0.193-0.399)	lifetime	0.1
Hemotoxic	Skin blisters and infection	Amputation	0.173 (0.118-0.240)	lifetime	0.05
Hemotoxic	Skin blisters and infection	Scarring from necrosis without amputation	0.011 (0.005-0.021)	lifetime	0.25
Neurotoxic	Skin blisters and infection	Amputation	0.173 (0.118-0.240)	lifetime	0.05
Neurotoxic	Skin blisters and infection	Scarring from necrosis without amputation	0.011 (0.005-0.021)	lifetime	0.25

Rate of CKD 5 incidence over CKD4 prevalence

Appendix Table 6. Ratio of stage five chronic kidney disease incidence over stage four chronic kidney disease prevalence in Bihar in 2019. Estimates were by sex, year, age, and location.

Age start	Age end	Sex	CKD5 incidence/CKD4 prevalence
0	0.019178	Male	1
0	0.019178	Female	1
0.019178	0.076712	Male	1
0.019178	0.076712	Female	1
0.076712	1	Male	1
0.076712	1	Female	1
1	4	Male	1
1	4	Female	1
5	9	Male	1
5	9	Female	1
10	14	Male	0.654627
10	14	Female	0.756139
15	19	Male	0.493272
15	19	Female	0.649556
20	24	Male	0.411323
20	24	Female	0.522755
25	29	Male	0.395517
25	29	Female	0.414818
30	34	Male	0.391907
30	34	Female	0.370587
35	39	Male	0.398607
35	39	Female	0.377118
40	44	Male	0.393808
40	44	Female	0.375721
45	49	Male	0.349025
45	49	Female	0.337774
50	54	Male	0.324058
50	54	Female	0.317366
55	59	Male	0.287137

55	59	Female	0.251142
60	64	Male	0.208746
60	64	Female	0.157021
65	69	Male	0.150412
65	69	Female	0.107652
70	74	Male	0.123401
70	74	Female	0.083141
75	79	Male	0.096172
75	79	Female	0.058813
80	84	Male	0.073462
80	84	Female	0.048326
85	89	Male	0.062938
85	89	Female	0.053048
90	94	Male	0.07054
90	94	Female	0.072961
95	99	Male	0.0996
95	99	Female	0.113541

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