Snakebite epidemiology in humans and domestic animals across the Terai region in Nepal: a multicluster random survey

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Summary

Background Each year, 2 million people worldwide are bitten by snakes, resulting in an estimated 81 000–138 000 deaths. WHO has added snakebite envenoming to the list of neglected tropical diseases, highlighting the need for stronger epidemiological evidence in endemic countries, such as Nepal.

Methods We conducted a cross-sectional survey in villages randomly geospatially selected from aerial images from across the Nepal's Terai lowlands region (excluding towns and cities). We collected data between Nov 30, 2018 and May 7, 2019, and analysed snakebite incidence rates and outcomes in humans and domestic animals.

Findings Among 63 454 human participants living in 13 879 households (249 villages), 166 were bitten by a snake over the previous 12 months; 48·8% were envenomed and 7·8% died. This corresponded to an annual crude incidence rate of 262 snakebites (adjusted incidence of 251·1 [95% CI 201·7–312·6]) and 20 deaths (22·4 [11·9–42·1]) per 100 000 people, extrapolating to 26 749–37 661 yearly bitten people and 2386–3225 deaths. Bitten people had a median age of 30 years (IQR 20–45) and with available data, 64% were female. Children younger than 15 years (n=6; 46%) and females (n=10; 77%) were disproportionately affected among the 13 people who died. The incidence was higher in the Eastern region, and mortality was higher in the Central region. Of 183 949 animals, owners reported 144 snakebites, with an annual incidence rate of 42–202 per 100 000 and mortality of 79–100%, varying by animal type. Spatial and seasonal incidence were similar in humans and in animals.

Interpretation This study provides the first epidemiological estimates of snakebite envenoming in humans and domestic animals across Nepal's Terai lowlands. It was also the first to use a community-based, transdisciplinary, and One Health design. These findings call for a strengthening of preventive measures and better access to life-saving treatments.

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Introduction

4–5 million people are estimated to be bitten by a snake each year, of which 2 million become clinically envenomed, 81 000 to 138 000 die, and another 400 000 suffer permanent disabilities.[1,2] In 2017, WHO included snakebite envenoming in its list of neglected tropical diseases, also publishing a strategic roadmap that called for large scale, population-based epidemiological studies.[3,4] The organisation highlighted the need for stronger epidemiological evidence in endemic countries, such as Nepal, to inform prevention and control strategies.

Snakebite envenoming is a major cause of hospitalisation and mortality in south Asia.[5] Large and nationwide surveys have been conducted in Sri Lanka[6] and Bangladesh,[7] improving authorities' awareness of snakebite envenoming as a public health priority and helping to optimise the allocation of resources. A nationwide study in India reported 58 000 annual snakebite envenoming deaths from 2000 to 2019.[8]

In Nepal, snakebite envenoming causes about 20 000 yearly hospital admissions and 1000 deaths, according to the Ministry of Health and Population and WHO, based on hospital-reported data from the past two decades.[9] Findings from community or hospital-based studies have shown a high snakebite envenoming incidence in Eastern,[10] Central,[11] and Western Terai.[12] These studies, although limited in scale and representativeness, showed high incidence, mortality, and disability due to snakebite envenoming, and the need for access to antivenoms, mechanical ventilation (in case of neurotoxic paralysis), and surgery (eg, fasciotomy and amputations). The Terai is the low altitude zone (<1000 m) of Nepal in the Ganges plain, with a typical monsoon warm tropical climate and predominant rice field agriculture. The hills (Pahad in Nepali) are moderately high mountains (up to 5000 m) and the mountains (Himal in Nepali) are the true Himalaya range with peaks beyond 8000 m with extremely cold temperatures (appendix, p 1). Both hills and mountains zones report very few snakebites victims.

See **Online** for appendix

Community-based surveys can better ascertain real incidence than hospital-based studies because out-of-hospital cases and deaths do not appear in hospital data.

Research in context

Evidence before this study

In its 2019 resolution on snakebite envenoming, WHO called for improved epidemiological evidence in endemic countries. In Nepal, hospital reports suggested that about 20 000 patients were admitted and 1000 died from snakebites each year. Available country reports and most research studies have relied on hospital-based data, which can underestimate the total burden of snakebite envenoming in the country. A study conducted in eastern Nepal in 2004 showed that 80% of bitten people died before reaching a medical facility. In this community-based study, conducted in four snakebite-prone villages, an alarming annual incidence of 1162 per 100 000 people was found. To date, no large-scale epidemiological studies have been done in Nepal's Terai and none has simultaneously analysed the effect of snakebite envenoming on both humans and domestic animals.

Added value of this study

This study provides the first epidemiological estimates of snakebite envenoming in humans and domestic animals across Nepal's Terai lowlands. In humans, reports show very high annual incidence rates (crude 262 per 100 000, adjusted 251 per 100 000) and mortality (20–22 per 100 000), and frequent long-term physical (eg, limb amputation) and psychological (eg, anxiety and phobias to return to the bite site) disabilities. This incidence could represent 26 749–37 661 people bitten by snakes and 2386–3225 deaths across the Terai. Snakebite envenoming incidence rates were higher in eastern regions, and mortality was higher in central regions. Children and women were over-represented among people who died. In domestic animals, we also found very high annual incidence rates (42–202 per 100 000) and mortality (79–100 per 100 000) varying by animal type, the highest incidence and mortality being in poultry and cattle. Spatial and seasonal incidence were similar in humans and animals.

Implications of all the available evidence

This study provides the first large scale epidemiological estimates of snakebite envenoming across Nepal's Terai lowlands, reporting very high annual incidence and mortality rates, as well as frequent physical and psychological sequelae. Incidence rates in children and women were particularly striking. These results call for strengthening of preventive measures and should contribute to improved deployment of, and patients' access to, life-saving treatments. To our knowledge, this is the first study of the dual effect of snakebite on human health and domestic animal health in the rural tropics, which could worsen the spiral of poverty induced by this neglected tropical disease of global health importance.

For various reasons (eg, long distance from hospitals, no access to transport, and reliance on traditional healers), people bitten by snakes often do not consult health facilities. In four selected villages of eastern Terai, most deaths occurred in the village (40%) or during transport to the treatment centre (40%), and only 20% occurred in the hospital.[10] These factors are well known causes of underestimation of snakebite envenoming incidence in hospital-based studies.[8,13] Nepalese medical authorities and national and international experts have advocated for a wider approach to snakebite envenoming, including large-scale national epidemiological surveys, aiming at defining regional incidence and estimating antivenom and medical staff requirements.[9]

The magnitude of snakebite envenoming of domestic animals (hereafter, animals) is unknown,[14] as comprehensive quantifications of the national, regional, or global burden of this problem are missing, including from Nepal and neighbouring countries. Considering the role of domestic animals as contributors to economic and social livelihoods of rural communities in snakebite-endemic areas, enhancing the understanding of the effect of snakebite in animals is also important as a global health and One Health priority.[14,15] Our One Health approach to snakebite is a transdisciplinary analysis of the human–animal–environment triad with the goal of better understanding the effect of the environment type and presence of domestic animals on the burden of snakebite on humans and the household economy. We aimed to estimate and describe the effect of snakebite envenoming on both humans and animals by conducting a large-scale community-based survey in Nepal's Terai, the most snakebite-prone ecosystem in Nepal.[9] In parallel, we also seek to understand the effect and characteristics of animal losses from the perspective of veterinary medicine.

Methods

Study design

We conducted a multicluster cross-sectional study across the Terai (covering seven Nepalese Provinces, all five former Regions), excluding towns and cities. Clusters, defined as village development committees (VDCs) in traditional Nepali administration, were used as primary sampling units. Households were the secondary sampling unit. We excluded small VDCs with fewer than 2000 inhabitants and large, urban VDCs (defined as more than 20 000 people). Detailed design and methods are published elsewhere.[16] In brief, we used cluster sampling with spatial random sampling of households based on satellite imagery, and in-depth analysis of household-level socioeconomic, environmental, medical, and animal health and production variables. Sample size calculation aimed at detecting a minimal annual incidence of 100 per 100 000 inhabitants during the past 12 months (0·1% prevalence, plausible limits of SD 0·05%), with a 99% confidence level, design effect for cluster heterogeneity of 2·0, and non-response margin of 15%. These criteria required 61 000 participants, or 13 864 households (4·4 people per household in Nepal), or 250 clusters of 55–56 households. Of 1436 Terai VDCs, we randomly selected 250 using a probability proportional to size sampling method, whereby each VDC has an individual probability-weight of its population divided by the total population of all VDCs. Within clusters (VDC), households were selected randomly from aerial images. The study was approved by the Nepal Health Research Council (Registration 585/2018), and the Commission Cantonale d'Ethique de la Recherche Scientifique in Geneva, Switzerland (CCER/SwissEthics Registry Number 2018-01331).

Procedures

Field data was collected by mobile teams between Nov 30, 2018 and May 7, 2019. A written informed consent form was obtained from each household (from the head of the household, usually the father or the mother of the family), plus another form for each person who was bitten by a snake, according to the victim's age (as per Nepal Health Research Council regulations). All interviews were done in Nepali or Hindi, helped by a local non-professional interpreter. Participants were administered e-questionnaires covering demographic, geographical, medical, veterinary, herpetological, and socioeconomical questions, directly uploaded to Kobotoolbox (a Harvard Humanitarian Initiative) from a tablet (XLS files available).[16]

Statistical analysis

Databases were imported from Kobotoolbox and curated in R (version 4.1.1). Statistical analyses were done in STATA/MP 14.1 (StataCorp). Descriptive, comparative statistics, and regression estimates considered the hierarchical nature and clustering effect of the design. We used the SVYSET function in STATA, after coding probability-weights for clusters and individuals, considering probability proportional to size sampling. We added a finite population correction based on the sample size and total population to adjust the variance estimates. Incidence rates were calculated as the cross-sectional prevalence of snakebite over the previous 12 months, per 100 000 participants, with 95% CIs, adjusted for cluster sampling. We applied prevalence to population per district from the Central Bureau of Statistics to derive regional estimates.[17] Household risk factors were assessed by univariate and multivariate logistic regression (odds ratios [ORs] unadjusted and adjusted for potential confounders). Classification of severity (ie, mild, moderate, and severe) and syndromes (ie, neurotoxic, haemotoxic, and cytotoxic) retrospectively determined by experienced clinicians (GA/FC) are shown in the appendix (p 2). Snakebites in animals were stratified into three categories: confirmed, probable, or suspected, through a standard operating procedure (appendix pp 3–4). Maps were developed in the open source geospatial tool QGIS (version 3.16). A rapid herpetological assessment of biting snake species used visual identification by victims compared with a photo album of 19 venomous and non-venomous snake species photos, names, and numeric codes (appendix pp 5–25).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Our study enrolled 63 454 participants living in 13 879 households in 249 clusters (VDCs). Only 17 households were not enrolled due to no consent. Non-availability

	Non-bitten participants (n=62 880)*	Snakebite cases (n=162)*	Deaths (n=13)
Age			
Median	27 (15–45)	30 (20–45)†	20 (9–35)†
Age group			
0–4	3991 (6·4%)	2 (1·4%)	0
5–14	11 621 (18·5%)	23 (15·5%)	6 (46·1%)
15–44	31 257 (49·7%)	80 (54·1%)	4 (30·8%)
45–59	9819 (15·6%)	26 (17·6%)	0
≥60	6172 (9·8%)	17 (11·5%)	3 (23·1%)
Sex			
Male	30 833 (49·1%)	52 (35·4%)	3 (23·1%)
Female	32 027 (50·9%)	95 (64·6%)‡	10 (76·9%)‡
Terai region			
Eastern	15 958 (25·4%)	58 (35·8%)	3 (23·1%)
Central	23 944 (38·1%)	52 (32·1%)	7 (53·8%)
Western	13 305 (21·2%)	32 (19·8%)	2 (15·4%)
Midwestern	7389 (11·8%)	18 (11·1%)	1 (7·7%)
Far Western	2284 (3·6%)	2 (1·2%)	0
Occupation or income			
Agriculture and farming§	35 398 (56·3%)	95 (58·6%)	5 (38·5%)
Daily worker, any job	9575 (15·2%)	34 (21·0%)	4 (30·8%)
Remittance	7084 (11·3%)	13 (8·0%)	1 (7·7%)
Shop, self-employed	5691 (9·1%)	11 (6·8%)	3 (23·1%)
Other employment	3729 (5·9%)	8 (4·9%)	0
Public employee	643 (1·0%)	0	0
Pension	523 (0·8%)	0	0
Other¶	114 (0·2%)	0	0

Data are n (%) or median (IQR). *Demographic data were missing for sex (n=19); age (n=18); region (n=4); occupation (n=5); and total (n=4). †p value <0·05. ‡p value <0·0001. p value is calculated by T test for continuous values, Mantel-Haenszel χ^2 for categorical and binary values, test-for-trend for age-groups (adjusted for clustering). All other p values are not significant. §Includes livestock breeding. ¶Includes fishing.

***Table 1:* Demographic characteristics of human snakebite victims and non-bitten participants**

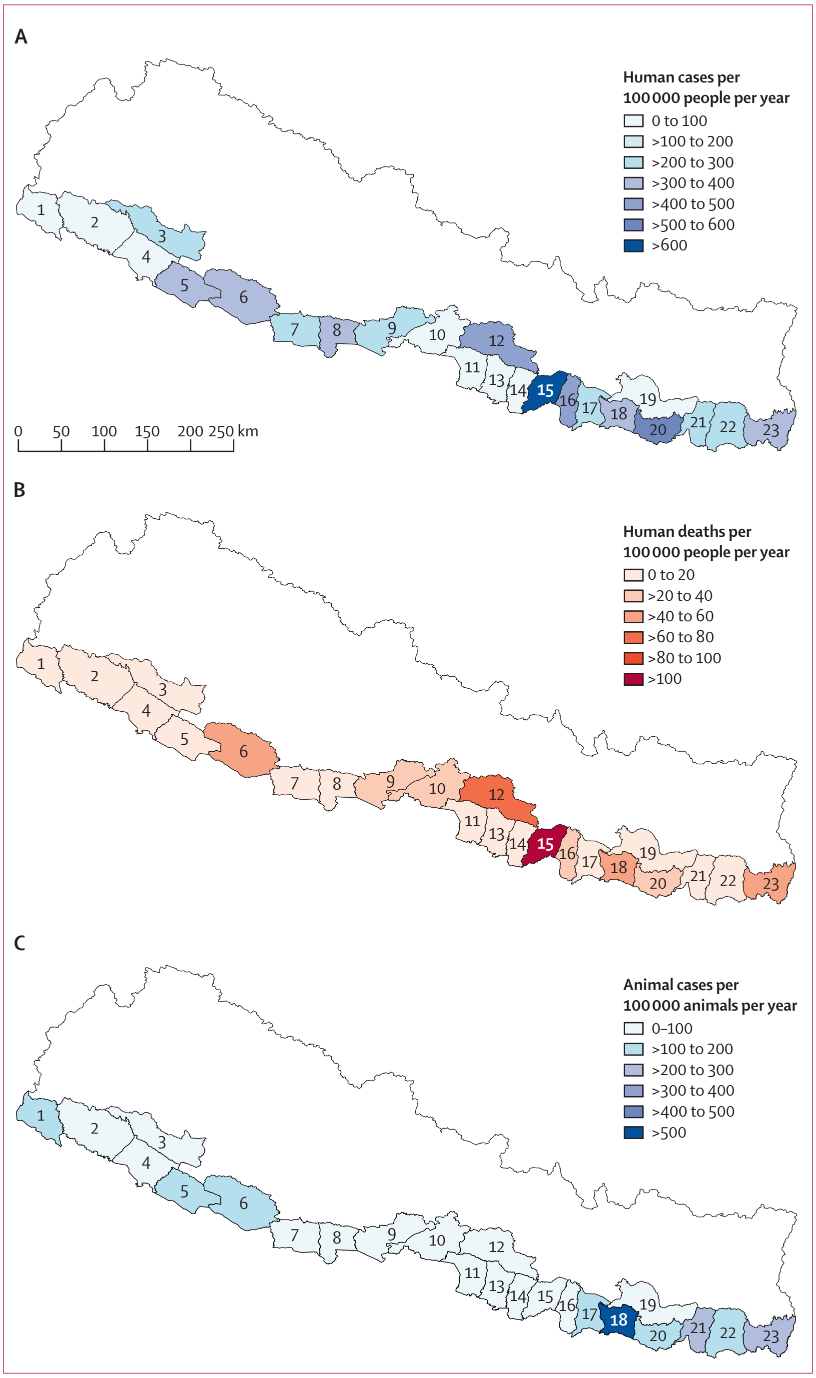

Figure: **District incidence and mortality of snakebite in humans and animals**
(A) incidence in humans, (B) mortality in humans, and (C) incidence in animals, which is almost equivalent to mortality in animals (not shown). The districts from west to east are: (1) Kanchanpur, (2) Kailali, (3) Surkhet, (4) Bardiya, (5) Banke, (6) Dang, (7) Kapilbastu, (8) Rupandehi, (9) Nawalparasi, (10) Chitawan, (11) Parsa, (12) Makwanpur, (13) Bara, (14) Rautahat, (15) Sarlahi, (16) Mahottari, (17) Dhanusa, (18) Siraha, (19) Udayapur, (20) Saptari, (21) Sunsari, (22) Morang, and (23) Jhapa.

(absent or empty households) was avoided by selecting an alternative household following a standard operating procedure. Of the initial 250 VDCs, one was not surveyed due to major damages after a storm and a state of emergency (Bara district; April, 2019). 166 people reported being bitten by snakes in the previous 12 months. Epidemiological stratification per district with bites and deaths was possible for bitten and not bitten participants. One or more missing values concerned 260 participants (<1%) including some demographic data missing from 19 affected people.

The median age of people bitten was 30 years (IQR 20–45, range 4–71). Non-bitten household members had a similar median age as bitten household members. The deceased snakebite victims' median age, 20 years, was significantly younger (IQR 9–35, $p=0·017$), and six (46%) of 13 individuals who died from a snakebite were aged 5–14 years (table 1). Excluding missing data, women were affected significantly more by snakebite envenoming than men, both in terms of cases and mortality ($p<0·0001$). Occupational profiles were not significantly different between victims and non-victims (table 1). Of the 13 879 households, 11 062 (79·7%) kept 183 949 animals. The types and numbers of animals owned by households are shown in the appendix (p 29). Animal ownership was high and homogeneous over the regions (75·3–89·7%), as shown in the appendix (pp 29–30).

Regarding human participants, among the 166 snakebite victims, 81 were envenomed (49%), and 13 died (case fatality rate 7·8%). Annual crude incidence rates of reported snakebite in humans was 261·6 per 100 000, and of death was 20·5 per 100 000. With adjustment for two-stage clustering the annual incidence was 251·1 (201·7–312·6) people bitten and 22·4 (11·9–42·1) deaths per 100 000. Based on Central Bureau of Statistics district population data, the estimated snakebite burden in all of the covered population was approximately 36 148–37 661 bitten individuals and 3225–2949 deaths per year (with or without cluster adjusted incidence rates), and 26 749 bitten individuals and 2386 deaths if we only consider strictly the VDCs with more than 2000 and less than 20 000 population, which is the most cautious minimalistic approach. The post-study design effect was 1·41, an acceptable figure for this cluster design. There was a higher proportion of victims in the Eastern and Central regions (provinces 1–3), than in the Western, Midwestern, and Far Western regions (provinces 4–7). Region-level incidences ranged from 80·1 (17·5–366·4) in the Far Western region to 330·1 (235·6–462·3) in the Eastern region (table 2). Among the 23 districts, the incidence ranged from zero to 678·0 per 100 000, with the highest in Sarlahi, Saptari, Mahottari (province 2), Makwanpur (province 3), Jhappa (province 1), and Dang (province 5; figure A).

Snakebite deaths per 100 000 ranged from 6·3 (0·8–48·8) to 40·5 (19·5–83·9) in provinces 1–5, but 0·0 in the Far Western Terai region (provinces 6 and 7; figure B). At the district level, very high mortality rates (above 40 per 100 000) were found in Jhapa and Siraha (province 1), Sarlahi (province 2), Makwanpur (province 3), and Dang (province 5).

	Number of VDC clusters	Total population	Participants	Snakebite cases in humans	Crude and adjusted incidence per 100 000 (95% CI)*	Crude and adjusted estimated total cases	Snake bite deaths	Crude and adjusted death rate per 100 000 (95% CI)*	Estimated total deaths
Eastern									
Province 1									
Morang	11	965 370	2440	5	204·9	1978	0	0·0	0
Sunsari	12	763 497	2858	6	209·9	1603	0	0·0	0
Jhapa	10	812 650	2431	9	370·2	3009	1	41·1	334
Udayapur	7	317 532	1444	2	138·5	440	0	0·0	0
Province 2									
Saptari	17	639 284	4845	28	577·9	3695	1	20·6	132
Siraha	9	637 328	2294	8	348·7	2222	1	43·6	278
Subtotal	..	..	16 312	58	355·6; 330·1 (235·6–462·3)	14 705	3	18·4; 15·3 (2·1–11·2)	761
Central									
Province 2									
Dhanusha	15	754 777	3269	7	214·1	1616	0	0·0	0
Mahottari	14	627 580	2975	12	403·4	2531	1	33·6	211
Sarlahi	16	769 729	3835	26	678·0	5219	4	104·3	803
Rautahat	16	686 723	3829	0	0·0	0	0	0·0	0
Bara	10	687 708	2054	0	0·0	0	0	0·0	0
Parsa	12	601 017	2472	1	40·5	243	0	0·0	0
Province 3									
Chitwan	15	579 984	3733	3	80·4	466	1	26·8	155
Makwanpur	7	420 477	1647	7	425·0	1787	1	60·7	255
Subtotal	..	..	23 814	56	235·2; 229·9 (150·0–352·1)	12 059	7	28·4; 36·4 (17·8–74·2)	1507
Western									
Province 4/5†									
Nawalparasi	12	..	3578	8	223·6	1413	1	27·9	177
Rupandehi	12	880 196	3966	12	302·6	2663	0	0·0	0
Kapilvastu	15	571 936	5986	12	200·5	1147	1	16·7	96
Subtotal	..	..	13 530	32	236·5; 223·7 (136·7–366·0)	4929	2	14·8; 8·9 (1·2–66·9)	308
Midwestern									
Province 5									
Dang	7	552 583	1717	6	349·4	1931	1	58·2	322
Banke	7	491 313	1905	6	315·0	1547	0	0·0	0
Bardiya	11	426 576	2760	3	108·7	464	0	0·0	0
Province 6									
Surkhet	5	350 804	1118	3	268·3	941	0	0·0	0
Subtotal	..	..	7500	18	240·0; 238·4 (146·4–388·0)	4371	1	13·3; 13·4 (1·7–10·3)	243
Far Western									
Province 7									
Kailali	6	775 709	1590	1	62·9	488	0	0·0	0
Kanchanpur	3	451 248	708	1	141·2	637	0	0·0	0
Subtotal	..	..	2298	2	87·0; 80·1 (17·5–366·4)	1068	0	0·0; 0·0	0
Total Terai									
Total rural population	249	14 395 943	63 454	166	261·6; 251·1 (201·7–312·6)	37 661; 36 148	13	20·5; 22·4 (11·9–42·1)	2949; 3225
Estimated only for VDCs with 2000–20 000 inhabitants	..	10 652 770	..	..	251·1 (201·7–312·6)	26 749	..	22·4 (11·9–42·1)	2386

Old Regions classification were used at the time of the study design; province classification is also indicated. VDC=village development committee. Design effect of 1·41. *Adjusted incidences (95% CI) for cluster-sampling methods. †Nawalparasi is now divided in Nawalparasi east and west, with respective populations of 310 864 and 321 058.

Table 2: **Snakebite incidence and mortality in humans in the Terai of Nepal by regions, province number, and district**

	Detailed clinical reports (n=150)	Dry or mild (n=69)	Moderate (n=38)	Severe (n=43)			
				Neurotoxic (n=32)	Haemotoxic (n=1)	Cytotoxic (n=6)	Unclear (n=4)
Region							
Eastern	59 (39%)	35 (59%)	2 (3%)	21 (36%)	0	0	1 (2%)
Central	45 (30%)	16 (36%)	19 (42%)	6 (13%)	1 (2%)	0	3 (7%)
Western	26 (17%)	14 (55%)	10 (39%)	2 (8%)	0	0	0
Midwestern	18 (12%)	3 (17%)	7 (39%)	2 (11%)	0	6 (33%)	0
Far Western	2 (1%)	1 (50%)	0	1 (50%)	0	0	0
Demographics by severity							
Age ≤15 years	27 (18%)	9 (13%)	7 (18%)	7 (22%)	0 (0%)	2 (33%)	2 (50%)
Sex females	97 (65%)	44 (64%)	21 (57%)	23 (72%)	0 (0%)	5 (83%)	4 (100%)
Limb bitten							
Foot, ankle, calf	93 (62%)	49 (71%)	22 (58%)	17 (53%)	0	5 (83%)	0
Knee, leg	17 (11%)	5 (7%)	8 (21%)	1 (3%)	1 (100%)	0	2 (50%)
Hand, wrist, arm	39 (26%)	15 (22%)	8 (21%)	13 (41%)*	0	1 (17%)	2 (50%)
Head, neck	1 (1%)	0	0	1 (3%)	0	0	0
Location							
Indoors	36 (24%)	20 (56%)	8 (22%)	7 (19%)	0	0	1 (3%)
Outdoor toilet	12 (8%)	5 (42%)	5 (42%)	1 (8%)	0	1 (8%)	0
Back yard, around house, or grain stock	36 (24%)	12 (33%)	10 (28%)	10 (28%)	0	2 (6%)	2 (6%)
On the road or track	14 (9%)	9 (64%)	1 (7%)	3 (21%)	1 (7%)	0	0
In the fields, pasture, or plantations	44 (29%)	19 (43%)	11 (25%)	10 (23%)	0	3 (7%)	0
In a river, stream, or flooded land	4 (3%)	3 (75%)	1 (25%)	0	0	0	0
In a forest	3 (2%)	0	2 (67%)	1 (33%)	0	0	0
Unknown	1 (1%)	1 (100%)	0	0	0	0	0
Activity or circumstance							
Working in field	60 (40%)	19 (26%)	23 (61%)	13 (41%)	0	3 (50%)	2 (50%)
Walking on path	32 (21%)	25 (36%)	1 (3%)	3 (9%)	0	3 (50%)	0
Herding animals	5 (3%)	1 (1%)	3 (8%)	1 (3%)	0	0	0
Resting	10 (7%)	5 (7%)	2 (5%)	3 (9%)	0	0	0
Playing	8 (5%)	3 (4%)	2 (5%)	3 (9%)	0	0	0
Sleeping on floor	4 (3%)	0	0	2 (6%)*	0	0	2 (50%)
Sleeping in bed	4 (3%)	1 (1%)	1 (3%)	1 (3%)	1 (100%)	0	0
Other (including fishing, n=4%)	27 (18%)	15 (56%)	6 (16%)	6 (19%)	0	0	0
Snake album (n=99%)†							
Colubrids listed‡	37 (37%)	16 (44%)	12 (30%)	5 (19%)	0	2 (50%)	2 (100%)
Cobras *Naja spp*	32 (32%)	6 (17%)	11 (37%)	15 (58%)§	0	0	0
Kraits *Bungarus spp*	23 (23%)	14 (39%)	3 (10%)	5 (19%)	1 (25%)	0	0
Pit Viper *Trimeresurus*	7 (7%)	0	4 (13%)	1 (4%)	0	2 (50%)	0

(Table 3 continues on next page)

Of the 166 people bitten, the clinical questionnaire was completed for 150 (90%), as shown in table 3. 69 (46%) people had dry or mild bites, 38 (25%) had moderate envenoming with some systemic signs (ie, malaise, nausea, vomiting), and 43 (29%) had severe envenoming. Among severe envenoming, 32 (74%) were consistent with neurotoxic effects (ie, ptosis, facial, or respiratory paralysis), six (14%) with cytotoxic effects (ie, extensive swelling, necrosis or shock), and one (2%) with haemotoxic (haemorrhage) envenoming, while four (9%) had an unclear clinical presentation. Only three victims reported neurotoxic signs without any pain or cytotoxic signs, possibly hinting towards a krait (*Bungarus spp*) bite. Most neurotoxic cases (21 of 32) occurred in the Eastern region. All severe cytotoxic cases were concentrated in the Midwestern region (6 of 6). One haemotoxic patient lived in the Central region. Severity and neurotoxicity were significantly more frequent ($p=0 \cdot 017$) in the Eastern and Central regions, and most snakebite cases were female ($p<0 \cdot 0001$), and

	Detailed clinical reports (n=150)	Dry or mild (n=69)	Moderate (n=38)	Severe (n=43)			
				Neurotoxic (n=32)	Haemotoxic (n=1)	Cytotoxic (n=6)	Unclear (n=4)
(Continued from previous page)							
Treatment							
None	60 (40%)	33 (48%)	15 (40%)	9 (28%)	0	2 (33%)	1 (25%)
Antivenom only	30 (20%)	7 (10%)	7 (18%)	15 (47%)¶	0	1 (17%)	0
Ventilation only	1 (1%)	0	0	1 (3%)	0	0	0
Antivenom & ventilation	6 (4%)	0	0	5 (16%)	1 (100%)	0	0
Other (various/traditional)	53 (35%)	29 (13%)	16 (42%)	2 (6%)	0	3 (50%)	3 (75%)
Surgery							
Amputation	5 (3%)	0	4 (11%)¶	0	0	0	1 (25%)
Debridement (necrosis)	7 (5%)	0	5 (13%)	2 (6%)	0	0	0
Repeated wound surgery >2 weeks	10 (7%)	0	1 (3%)	5 (16%)¶	0	3 (50%)	0
Short surgery <2 weeks	5 (3%)	0	0	4 (13%)	1 (100%)	0	0
No surgery	124 (83%)	69 (100%)	28 (74%)	21 (66%)	0	3 (50%)	3 (75%)
Final outcomes							
Death||	10 (7%)	0	0	6 (14%)	0	0	4 (100%)
Disability walking||	20 (13%)	6 (9%)	4 (11%)	6 (20%)	0	4 (67%)	0
Disabled arm/hand||	15 (10%)	4 (6%)	2 (5%)	6 (20%)	1 (100%)	1 (17%)	1 (25%)
Anxiety-phobia||	14 (9%)*	0	2 (5%)	5 (17%)	0	0	0
No disability	114 (77%)	59 (86%)§	30 (79%)	14 (47%)	0	1 (17%)	3 (75%)

*p value ≤0·05. †Snake seen in 71% of cases (106/150). ‡Includes one bitten in toilet classified as moderate. §p value ≤0·001. ¶p value ≤0·01. ||Multiple disabilities are possible for the same individual (only ten of 13 deaths could be described) total beyond n=150, not cumulative.

***Table 3*: Clinical outcomes and bite circumstances of humans bitten by snakes**

most neurotoxic cases were female (23 [72%] of 32). Nearly three-quarters (73%) of people were bitten on lower limbs (110 of 150) and 63% were bitten below the knee (ie, foot, ankle, or calf; 93 of 150), while working in the field (60 [40%] of 150) or walking on a path (32 [21%] of 150; table 3). About half (22 [51%] of 42) of severe, neurotoxic, and lethal snakebites occurred on the foot and ankle. However, bites to upper limbs were significantly associated with neurotoxicity (OR 2·25 [95% CI 1·0–5·0], p=0·016). Victims received first-aid most frequently in the community (114 [77%] of 148), and less frequently at a health post (four [3%]) or hospital (30 [20%]). Regarding treatments, of 150 victims, 116 (77%) received traditional first-aid treatment such as suction, tourniquets, herbs, chili, mustard oil, or prayers. 90 (60%) patients eventually reached a medical facility, with clinical features of severe (n=31), moderate (n=23), or mild (n=36) envenoming. Among them, 36 patients (40%) received antivenom, including 22 with severe envenoming, seven with moderate envenoming, and seven with mild envenoming. Seven (8%) patients received mechanical ventilation, with or without antivenom. None described renal dialysis.

Antivenom treatment was associated with severe envenoming, but a third of patients who received antivenom described non-severe symptoms and signs (22 of 36 *vs* 12 of 36, p=0·012). Among severe patients, lethality was lower for those who had received antivenom than for those who did not (three [14%] of 22 *vs* five [56%] of nine, p=0·015). Among the seven ventilated patients, five survived.

Severe envenoming was strongly associated with surgical complications (16 [37%] of 43 *vs* ten [9%] of 107, p<0·0001). Local complications required amputation in five (4%) of 136 bitten individuals and other surgical interventions in 22 victims (16%). Sequelae occurred in 34 (23%) of 148 victims, such as walking disability (31 [21%]), arm-hand function disability (15 [10%]), persistent stress or anxiety preventing normal work, inciting nightmares, or phobia (fear) to return to the bite location, or a mix of them (n=16, 11%). Disabilities were more frequent for patients with severe envenoming (23 [56%] of 41 *vs* 18 [17%] of 107, p<0·0001), but also occurred with mild (ten [15%] of 69) or moderate (eight [21%] of 28) snakebites. Deaths were associated with neurotoxic syndromes, and was also associated with young age (5–14 years, p=0·006) and was more frequent among female gender (p<0·0001).

Regarding herpetology, 106 [71%] of individuals bitten saw the biting snake, and almost all of these (99 [93%]) recognised the species in the precoded photo album. Cobras (*Naja* spp) were frequent (32 [32%]) and were associated with severity (p=0·009) and neurotoxicity (p=0·012). Kraits were the next most common neurotoxic snake (23 [23%]). The remainders were colubrids (37 [37%]) and pit vipers (7 [7%]).

	Presence of risk factor (%)	People bitten by snake with this factor (%)	Univariate OR (95% CI)	p value	Multivariate* adjusted OR (95% CI)	p value
Food storage in the house	11 429 (81·6)	153 (94·4)	3·72 (1·73–8·05)	0·001*	1·88 (0·99–3·57)	0·054
Animal shed	9635 (68·8)	124 (76·5)	1·32 (0·73–2·04)	0·34	..	..
Straw or wood house	7683 (54·9)	117 (72·2)	2·14 (1·41–3·23)	<0·0001†	1·61 (1·08–2·41)	0·02
Sleeping on the floor	626 (4·5)	8 (4·9)	1·10 (0·40–3·03)	0·85	..	..
No use of mosquito net	298 (2·1)	2 (1·2)	0·60 (0·17–2·12)	0·44	..	..
Use of outdoor toilet	9839 (70·3)	101 (62·4)	0·68 (0·42–1·12)	0·13	0·77 (0·52–1·12)	0·17
Open defecation	1713 (12·2)	17 (10·5)	0·99 (0·53–1·84)	0·97	..	..
Household size five plus people	6189 (44·2)	121 (74·7)	2·13 (1·48–3·08)	<0·0001†	1·90 (1·33–2·72)	0·004
Kept animals in the past year	11 153 (79·7)	151 (93·2)	3·13 (1·44–6·81)	0·004†	1·50 (0·73–3·08)	0·27
Kept poultry in the past year	3256 (29·2)	33 (21·8)	0·68 (0·45–1·03)	0·06	..	..

OR=odds ratio. *Univariate and multivariate models were adjusted for cluster survey (svyset) methods with cluster weights. †Multivariate model included age, sex, and the four household variables with an univariate $p<0·05$.

Table 4: **Household related risk factors for snakebite in humans (n=162)**

	Number of cases*	Incidence per 100 000 (95% CI)	Herds with animal cases	Herd-level† incidence rate (in %); (95% CI)	Number of animals[18]	Animal bitten by snakes per year (95% CI)
Poultry	80	66·2 (53·2–82·4)	43	1·321 (0·982–1·775)	50 055 678	33 140 (26 630–41 240)
Cattle or buffalo	15	62·0 (37·6–102·3)	15	0·183 (0·111–0·301)	7 480 134	4639 (2812–7653)
Goat	13	41·6 (24·3–71·1)	13	0·183 (0·107–0·312)	5 075 494	2109 (1233–3609)
Sheep	1	202·4 (35·7–1138)	1	0·826 (0·146–4·533)	133 536	270 (47·7–1519)
Dog	1	196·9 (37·8–1106)	1	0·270 (0·048–1·515)	NA	NA
Horse or donkey	0	0	0	0·000	4539	0
Pig	0	0	0	0·000	661 275	0
Cat	0	0	0	0·000	NA	NA
Total	110	61·5 (51·0–74·1)	73	0·65 (0·521–0·822)	63 410 656	38 616 (32 020–46 570)

NA=Not available. *Cases are confirmed plus probable (ie, without suspected cases). †Herd is defined as a group of animals of the same type that belong to a household.

Table 5: **Snakebite incidence in the Terai by domestic animal type**

All children younger than 8 years of age (n=4) and most children younger than 15 years (14 [56%] of 25) were bitten indoors or in the yard (table 3). The proportion of women bitten indoors or around the household was higher (58 [60%] of 97) than that of men (26 [50%] of 52). Ten potential household risk factors collected in the questionnaire were included in our regression model with clustering adjustment. At first, four factors seemed significantly associated with the risk of snakebite in the univariate logistic regression model (table 4): having straw or grain or food storage, keeping animals during the past year, or a household size above five people. In the multivariate logistic regression, two variables remained significantly associated with risk: having straw storage (adjusted OR 1·6 [95% CI 1·08–2·41]) and household size above five people (OR 1·9 [1·33–2·72]). We found no association between these two risk factors and bites occurring in the household vicinity.

Among the 11 062 households keeping animals, 93 (0·8%) reported 144 animals bitten by snakes during the 12 months preceding the survey, predominantly in poultry (n=99, 69%), cattle (n=22, 15%), and goats (n=21, 15%). Most households (82 [88%] of 93) reported only one snakebite for their animals, but 11 (12%) of 93 reported multiple cases (two to 30) affecting the same type of animal (eg, only poultry) or multiple types (eg, chicken and cattle) in the same or distinct episodes. Most animal snakebites were classified as confirmed or probable (n=110; 76·4%), yielding an annual incidence ranging from 41·6 to 202·4 per 100 000 depending on the animal type (table 5).[18] As a retrospective diagnosis of snakebite in animals is problematic due to numerous differential diagnoses, we excluded suspected bites from the incidence calculation. When extrapolated to the population level, this number translated into 38 616 (95% CI 32 020–46 570) potential animal victims in the Terai annually. The highest incidence was found in Eastern (eg, Sunsari and Jhapa districts) and Midwestern (eg, Dang and Banke districts) regions (figure C, all animal types combined; appendix pp 29–31). Mortality due to snakebite was high, ranging from 78·6% in cattle to 100% in poultry (appendix p 32). Snakebite in humans and animals did not overlap in the same households.

The seasonality of snakebite in humans and animals partly overlapped (appendix p 32). We observed clear peaks during monsoon months (May–September) when both rainfall and temperature are higher.

Discussion

We report the results of the first snakebite epidemiological study conducted in Nepal that covered the entire rural Terai, applying an original methodology that included a One Health approach. Geospatial sampling was previously used in one national survey in Sri Lanka,[6] and other large representative studies were performed in Bangladesh[7] and India,[19] using different methods; however, none included an animal health component.

We found a very high adjusted annual incidence rate (251 per 100 000), envenoming rate (49%), and case-fatality rate (7·8%) overall in humans. Unlike previous studies in Nepal,[10,11,20] which focused on a restricted number of districts or villages with incidences up to 1162 per 100 000,[10] our random sample reliably represented the entire rural population of the Terai (ie, 14·4 million people), more precisely the 10·6 million living in VDCs with a population of 2000 to 20 000 people (ie, the VDC population range included in our survey). This representation allowed us to cautiously estimate the burden of snakebite in the Terai (approximately 26 749–37 661 snakebite cases, including 2386–3225 deaths), and its geographical distribution, informing local health policies and antivenom supply, while also considering seasonality. We identified two independent risk factors of snakebite at the household level—ie, having straw storage, and household size above five people. The latter factor is a proxy of poverty, strongly associated to snakebite and neglected tropical diseases.[21]

The metaphor "neglected tropical diseases are the landmines of public health"[22] holds particularly well for people affected by snakebite, as these accidents often occur by stepping on a snake. We found that three-quarters of victims were bitten on a lower-limb, and two-thirds below the knee. Possible prevention measures include walking with a source of light, clearing high grass around the house, and use of appropriate footwear—ie, favouring shoes instead of sandals and favouring boots for high-risk activities.

More than half of snakebite victims reported systemic symptoms, and 29% were graded as severe (most frequently neurotoxic), mostly associated with bites from cobra (*Naja spp*) and krait (*Bungarus spp*), as identified by the bitten individuals from a photo album. However, identification of snakes by victims, especially weeks or months after the event, is notoriously imprecise.[23]

Two-thirds of victims accessed medical facilities, half were severely envenomed, but only half of these received antivenom, due either to poor availability or suboptimal prescription practices. Among patients with severe envenoming, death and disability was significantly lower among patients who received antivenom than those who did not, and among ventilated patients. However, antivenom was given to a third of patients who reported no severe clinical symptoms, highlighting the need to avoid antivenom wastage.

The extent of amputations, surgery, and disabling sequelae is striking, indicating a need for physiotherapy, orthopaedics, and chronic wound care. These patients could be integrated in foot-care programmes dedicated to patients with diabetes and leprosy. Finally, the high frequency of reported psychological symptoms, such as anxiety or fear to return to the accident site, highlights the need for mental health support. Such psychological sequelae have been described in more detail in Sri Lanka, with increased risk of depression and post-traumatic stress disorder.[24]

In our study, the group of children aged 4–15 years represented almost half of the deadly snakebite envenoming. Children are particularly susceptible because a smaller distribution volume of the injected venom results in higher rates of severity, necrosis, and disability than in adults.[25,26]

Women and girls made up three-quarters of deaths in our survey. This unexpected finding contrasts with previous studies in eastern Nepal that identified a majority of males,[10,20] with up to 73% in a study of 4078 hospitalised patients.[27] Potential causes for an increased risk of snakebite (eg, activity or type of footwear) and mortality (eg, differential access to treatment or smaller body mass) in females should be investigated.

The global burden of snakebite envenoming in animals is unknown.[14] We found a high incidence and mortality in several animal types, particularly poultry, cattle, and goats. Animal production practices, such as free-grazing and open-sided covered shelters with dried grass forage, expose animals to snakes, as shown in a study in 1998 that highlighted snakebite dangers for livestock in the Terai.[28] Nepal is predominantly agricultural, with 80% of its population depending on this activity for their livelihood.[29] Thus, animal losses due to snakebite can have a strong impact on livelihoods and add to the burden of snakebite in humans. We will report the socioeconomic effect of both human and animal snakebite in a separate publication. Our data could help to develop intersectoral strategies on snakebite envenoming including interactions in Nepal between Ministries of Health and Population, Agriculture and Livestock Development, Forests and Environment, and corresponding UN agencies (eg, WHO, UNICEF, FAO, and UNEP).

Regions with a higher incidence of snakebite in humans and animals overlapped in parts of Terai (eg, Eastern and Midwestern regions) suggesting snakebite hotspots. A better understanding of socioecological factors favouring these snakebite hotspots is essential for optimised prevention strategies. In Bahia, Brazil, snakebite incidence in humans was strongly associated with agricultural practices, cocoa and coffee plantations, or numbers of chickens and livestock.[30,31] We also found that keeping animals directly or indirectly increased snakebite envenoming risk in humans. Improved community-level awareness and activities could also reduce mortality, as shown by a snakebite motorbike project in Eastern Nepal.[32]

There are several limitations in our study. Some degree of recall bias always occurs in cross-sectional studies using retrospective incidence.[33] We believe that recall bias was reduced by the inherent strong memory left by a snakebite, a traumatic event,[24] and mitigated by using events in the Nepali calendar as time references. Deaths among heads of households would not bias the probability of selection because spouses ("other relatives") were also considered as heads of households and were interviewed. The incidence was measured over one year to accommodate seasonal (monsoon) variation. We do not expect significant supra-annual variation, but our study does not address this. A small limitation results from the selection of rural areas, excluding the small proportion of snakebite envenoming occurring in urban, hills, and Himalayan areas. Regarding incidents involving domestic animals, we did not sample by species, and we used the human-based sample size for the design. A recall bias towards severe bites is likely, possibly explaining the high mortality in animals. Thus, we suspect an under-estimation of incidence in animals.

This study provides the first epidemiological estimates of snakebite envenoming across Nepal's Terai lowlands, reporting an alarming adjusted annual incidence rate of 251 per 100 000, associated with high mortality and mental and physical sequelae. Incidence and deaths among children and women were disproportionately high. Several targeted preventive measures could mitigate this high effect of snakebite in the Terai, such as population awareness campaigns, improved training of health professionals, better deployment, rapid access to lifesaving antivenoms and respirators, and early clinical management of sequelae. Animal losses due to snakebite add to this burden in humans and call for cross-sectorial One Health actions.

Contributors

All authors contributed to the conceptualisation and the general method. FC and NR led the Snake-BYTE project and acquired the funding. GA conceptualised the epidemiological analysis, co-organised the training and pilot in Nepal, did the statistical analyses, produced estimates and tables, and wrote the first manuscript draft under the supervision of FC and NR. SKS led the field investigation and administration. SKS, MS, AG, BS, GA, CO, FC, NR, IB, and SBM co-organised the training and pilot in Nepal and co-supervised the field work (investigation) and data collection in Nepal. IB conceptualised the animal epidemiological analysis, survey methods, and produced estimates and tables. IB, SBM, CO, GA, and RRdC supported the One Health epidemiological approach. CO produced the geospatial analysis resulting in incidence maps based on incidence estimates produced by GA and IB. EG, CO, GA, and FL contributed to epidemiological and geospatial software (kobo-collect, Guru maps, and QGIS) and specific survey methodology. Data were curated by CO and GA. All co-authors discussed the results, reviewed and validated the drafts, interpreted the findings, and had access to all the study data. GA and SKS contributed equally as first authors.

Declaration of interests

We declare no competing interests.

Data sharing

For the primary data collected in the Snake-Byte survey, participant data that underlie the results reported in this article will be made available on reasonable request through the University of Geneva data repository, after de-identification, beginning 12 months following the publication of this article. Requests should be directed to nicolas.ray@unige.ch.

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