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Trends in snakebite deaths in India from 2000 to 2019 in a nationally representative mortality study

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Abstract

The World Health Organization call to halve global snakebite deaths by 2030 will require substantial progress in India. We analyzed 2,833 snakebite deaths from 611,483 verbal autopsies in the nationally representative Indian Million Death Study from 2001-14, and conducted a systematic literature review from 2000-19 covering 87,590 snakebites. We estimate that India had 1.2 million snakebite deaths (average 58,000/year) from 2000-19. Nearly half occurred at ages 30-69 years and over a quarter in children <15 years. Most occurred at home in the rural areas. About 70% occurred in eight higher-burden states and half during the rainy season and at low altitude. The risk of an Indian dying from snakebite before age 70 is about 1 in 250, but notably higher in some areas. More crudely, we estimate 1.11-1.77 million bites in 2015, of which 70% showed symptoms of envenomation. Prevention and treatment strategies might substantially reduce snakebite mortality in India.
Introduction
The World Health Organization (WHO) estimates that 81,000-138,000 people die each year from snakebites worldwide, and about three times that number survive and but left with amputations and permanent disabilities [WHO, 2019a]. Bites by venomous snakes can cause acute medical emergencies involving shock, paralysis, hemorrhage, acute kidney injury and severe local tissue destruction that can prove fatal or lead to permanent disability if left untreated. Most deaths and serious consequences from snakebite envenomation (exposure to venom toxins from the bite) are avoidable by timely access to safe and effective antivenoms [Gutiérrez et al., 2017]. Snakebite deaths and envenomation are largely neglected topics in global health. However, in 2017, the WHO included snakebite envenoming in the priority list of neglected tropical diseases [WHO, 2019b] and launched in 2019 a strategy for prevention and control of snakebite, aiming to halve the numbers of deaths and cases of serious disability by 2030 as compared to 2015 baseline [WHO, 2019c]. Achieving this goal will require substantial progress in India, which is home to approximately half of global snakebite deaths. Snakebite deaths and disability remain a major public health challenge also for poor rural communities in many parts of Asia, Africa, Latin America and Oceania.

Direct estimation of 46,000 annual snakebite deaths in India in 2005 [Mohapatra et al., 2011] prompted a revision of the WHO’s global total, which had estimated about that many for the entire world. The 2005 Indian estimate relied upon analyses of about 123,000 verbal autopsy records from 2001-3 in the Registrar General of India’s (RGI) Million Death Study (MDS), one of the largest nationally representative mortality surveys. Now the MDS has reported cause-specific mortality patterns on over 600,000 deaths from 2001-14 for the whole of India. Here we report seasonal and temporal trends in snakebite mortality over the last two decades in India and its spatial distribution. We provide estimates of total snakebite deaths for the 20-year period 2000-2019 by age and sex. Our earlier report estimated a crude ratio of about one death to 20 envenomations. We now further quantify the levels of envenomations based on a systematic review of 81,000 snakebites in the published literature. The literature also provides details on the specific causes, bite locations, and treatment of envenomations. Finally, enhanced surveillance including facility-based tracking will be central to the Government of India’s strategies to reduce snakebite deaths. Thus, we provide some estimates on the degree to which snakebites and deaths are reported adequately in public facilities. Appendix 1-figure 1 shows the overall study design, data sources, input resources and outcomes.

Results
Trends in snakebite mortality and its geographic and temporal patterns
From 2001 to 2014, the MDS reported deaths with causes classified by physicians who examined verbal autopsy records collected from over 3.6 million households in three distinct nationally-representative sampling frames (1993-2003; 2004-13; and 2014-23). Two of 404 independent physicians coded each death to the International Classification of Diseases-10th revision (ICD-10), reconciling (anonymously)
any coding differences with a senior physician adjudicating any persistent disagreements [Gomes et al.,
Aleksandrowicz et al., 2014; Menon et al., 2019]. Among 611,483 available records, 2,833 deaths
were assigned to snakebites (ICD-10 code X20). The two physicians agreed on the diagnosis 92% of the
time. About 94% of snakebite deaths occurred in rural areas, and 77% occurred out of hospital
(Appendix 1-table 1).

We applied the age- and sex-specific proportion of snakebite deaths to total deaths as estimated by
the United Nations Population Division (UN) for India [United Nations, 2019] to estimate national
death rates by age and sex, as well as absolute totals for each year (Table 1). The UN totals are based
on careful demographic review of census and other data sources. The fieldwork procedures of the
Sample Registration System (SRS the underlying demographic survey on which the MDS is based) leads
to some undercounts (of about 5-10%) of expected deaths [Gerland P. 2014]. The SRS is representative
at the state and rural/urban strata, and has a large, distributed sampling covering over 7,000 small
areas in the whole of the country [Registrar General of India, 2017]. Hence, any missing deaths are
generally randomly distributed across states, and not clustered in one state or one key sub-group, such
as in rural areas [Dhingra et al, 2010; Aleksandrowicz et al., 2014; Menon et al., 2019]. Thus, the
proportion of snakebite deaths is not likely an underestimate. However, total snakebite deaths might
be underestimated. The use of the UN death totals adjusts for these possible undercounts, and
provides a plausible national total for each year.

Total snakebite deaths in India from 2001-14 totaled about 808,000, with reasonably narrow
uncertainty range of 738,000 to 833,000, based on both physicians immediately assigning snakebites
or one physician doing so. Some age-specific death rates fell, but as population growth averaged 1.1%
annually, the application of annual age-specific rates to the UN death totals for that year showed that
the overall number of snakebite deaths grew from about 55,000 in 2001 to about 61,000 in 2014.
During the 2001-14 MDS study period, the average age-standardized snakebite death rate (using the
Indian census population of 2001 to take into account the minor change in age structure) was 4.8 per
100,000 population, falling annually by 0.8%.

Declines in the age-specific snakebite death rate were fastest for children aged 0-14 years (declining by
about 1.6% annually), with slower declines in young adults aged 15-29 years (1.2% annually) and no
decreases among middle-aged adults (30-69 years). Before 2010, snakebite death rates were higher in
boys than girls but from 2010-14, death rates in girls exceeded those for boys (Appendix 1-table 1). The
age-specific risks translate to a probability of 0.37% (uncertainty range 0.34%-0.38%) of dying from
snakebite before age 70 years in the absence of competing mortality (Table 1). This suggests that the
average risk of an Indian dying from snakebite prematurely before age 70 is approximately 1 in 250.
Because the risk of dying from snakebites has been stable from 2001-14, we can make reasonable forward projections from 2015 to 2019 and backward projections from 2001 to 2000 (Table 2). This reveals that 1.167 million snakebite deaths occurred over this 20-year period. Of these deaths, 602,000 occurred among males and 565,000 occurred among females. With both sexes combined, about 543,000 (47%) occurred in middle-age (30-69 years), 325,000 (28%) among children below 15 years, 197,000 (17%) among adults aged 15-29 years, and 102,000 (9%) among those over age 70 years. The main uncertainty in these estimates is not the demographic denominators, but the classification of the cause of death as snakebite. Using the agreement of one or two physicians on the cause, yielded generally narrow uncertainty estimates for each sex and age groups.

From 2001-14, just under 70% of these snakebite deaths occurred in eight states with about 55% of the population: Bihar, Jharkhand, Madhya Pradesh, Odisha, Uttar Pradesh, Andhra Pradesh (which includes Telangana, a recently defined state), Rajasthan and Gujarat (Table 3). In these high-burden states, the age-standardized death rate was about six per 100,000. Snakebite death rates generally rose over time in most high-burden states, particularly in Bihar, but fell in Andhra Pradesh. The remaining lower-burden states began the study period with age-standardized death rates of about 3.7, which fell over time. Figure 1 shows the absolute risk of dying from snakebite using data from 7,400 small areas (the small sampling units used in the RGI’s Sample Registration System for the MDS) from 2004-13. The absolute risks were calculated applying spatially-smoothed predictive relative risks from a spatial Poisson model to the overall national risk before age 70 years (of about 0.4%, Table 1) after adjusting for any differences in rural/urban status, female illiteracy levels, temperature, and altitude of local areas. We observed greater than 0.6% (1 in 167) mortality risk before age 70 years in the highest risk sub-areas of Andhra Pradesh, Odisha, Bihar, Uttar Pradesh, Madhya Pradesh, Chhattisgarh, and Rajasthan. About 260 million people lived in these areas in 2015, including about 4 million in hot spots that had a 1% or greater risk of death from snakebite. Appendix 3 provides statistical details and credible intervals of these risk estimates.

Half of all snakebite deaths occurred during the southwest monsoon seasons from June to September. Seasonality was similar in each of the study years (Appendix 1-figure 2) and was similar in higher-burden and lower-burden states (data not shown). We used a Poisson time series model for snakebite deaths from 2001 to 2014 to predict the average daily snakebite mortality in India. The peak (294 deaths per day) was in mid-July and the trough (78 deaths per day) was in mid-February (Figure 2A). We also aggregated the deaths from 2001-13 by every 100 meters of altitude above sea level (Figure 2B). The crude death rates in areas below 400 meters were about three times those in areas at about 1000 meters. Over 80% of snakebite deaths occurred below 400 meters and 50% occurred below 200 meters.

Characteristics of snakebites from a systematic review of the literature
A systematic literature review yielded 87,590 snakebite cases in India (both fatal and non-fatal) from 2000-19 based on screening 1,417 papers and including 78 studies from 24 states or union territories in India (Figure 3, Appendix 2-figure 1, Appendix 2-table 2). In the published studies, snakebites were more common in males (59%), at ages 30-69 years (57%), from June to September (48%), and occurring outdoors (64%). These results match the relevant results for the MDS. However, MDS snakebite deaths were equal between males and females. The leg was the dominant site of bite (77%), and the time of reported bite was throughout the day. Of the treated cases, nearly two-thirds (66%) were seen within 1-6 hours, with the remainder seen after six hours. The proportion treated within 1-6 hours improved over time (data not shown). In the limited sets of studies that attempted to identify the snake species, Russell’s viper (Daboia russelii) constituted 43%, followed by unknown species (21%), krait (Bungarus species) (18%), and cobra (Naja species) (12%).

Snakebite and mortality surveillance
The Government of India relies on reporting via public hospitals to track snakebites and deaths [GOI, 2015]. We examined the total bites and deaths available from 2003 to 2015 in Government hospitals and compared these deaths to the MDS in-hospital deaths (Table 4). Over this 13-year period, the MDS estimated about 154,000 snakebite deaths in public and private hospitals, and the Government reported 15,500 deaths in hospitals, meaning that the routine reporting system captured only 10% of the expected hospital-based deaths. The most complete reporting was in Karnataka at 26%.

Snakebite prevalence and envenomation
Among the 87,590 snakebites reported in the literature, there were 3,329 reported deaths (Appendix 2-table 1). We fitted death and bite data from each study to an ordinary least square regression to calculate a case-fatality rate, after removing the extreme outliers. We estimated a crude case-fatality rate of 3.2% for in-hospital cases. Based on mostly cautious assumptions about the ratio of in-hospital to out-of-hospital prevalence of snakebites (Appendix 1-table 2), we estimate the total number of snakebites to range from 1.11 to 1.77 million in 2015. Based on 44 hospital studies where 70% of patients sought treatment, were diagnosed with systemic envenomation, and received antivenom, we estimate that the annual number of envenomations is about 0.77 to 1.24 million with the remainder being “dry bites” or bites by non-venomous species (0.33 to 0.53 million).

Discussion
Our nationally representative mortality study documents about 1.2 million snakebite deaths from 2000-19. Most occurred at home in the rural areas. About 70% occurred in eight higher-burden states and half occurred during the rainy season and in low altitude rural areas. While rates of childhood and young adult snakebite mortality have fallen, those in middle age have not. Thus, the average risk of an Indian dying from snakebite before age 70 is approximately 1 in 250, but in some areas, this risk approaches 1 in 100. Over 260 million Indians live in areas of moderate risk of about 1 in 167. More
crudely, approximately 1.11-1.77 million bites occur annually with about 70% representing envenomation, and 58,000 dying. While snakebite deaths represent only about 0.5% of the approximately 10 million deaths that occurred in India in 2015, they are nonetheless important, as they are nearly all avoidable.

Many of the features of snakebites and deaths were known or suspected, but few were quantified reliably [Mohapatra et al., 2011]. Our study’s novel contributions are to quantify some of these features, and identify other findings that are relevant to improved epidemiological understanding and to prevention and treatment in snakebite control programs. The map of the snakebite mortality risk (Figure 1) highlights ‘hot spots’ in each state, which are at lower altitude. This reflects not only the more highly populated and the more extensive and intensively farmed arable land at lower altitudes, but also the species and population densities of snake species of medical importance. These snake densities are sometimes very high, particularly in grain agriculture which attracts the largest rodent and amphibian populations that are eaten by snakes [Whitaker and Captain 2004; Mise et al, 2016].

Focusing on agrarian communities in specific areas which carry the highest risk of mortality, especially during the monsoon seasons, could reduce mortality and morbidity attributable to snakebites. Targeting these areas with education about simple methods, such as ‘snake-safe’ harvest practices, wearing rubber boots and gloves and using rechargeable torches (or mobile phone flashlights) could reduce the risk of snakebites. Mass distribution of mosquito nets (which also protect against scorpion sting and mosquito-borne diseases) is a relevant strategy that could build upon the National Vector Borne Disease Control Program’s efforts to control malaria, kala-azar, and arboviral infections.

Our study has implications for better treatment, particularly in the distribution of effective antivenom to the areas and populations in greatest need. Increased use of antivenom would require tactful cooperation with local traditional healers and ayurvedic practitioners to persuade them to refer severely ill patients for treatment with antivenom, and raising awareness of the effectiveness of antivenom. Government hospitals should make antivenom freely available to snakebite victims [Whitaker and Whitaker 2012]. Health services should monitor adverse reactions to antivenom and improve distribution and cold-chain storage, matching supply to places and times of greatest need.

Training of local medical staff and emergency responders should be improved so that they can administer antivenom by intravenous injection and also identify and treat early anaphylactic reactions. India has sufficient manufacturing capacity for large snake antivenom production. Better understanding of the distribution of India’s many venomous snake species could help in the development of more appropriate antivenoms. The current Indian polyvalent antivenoms neutralize venom from only common cobra (Naja naja) (there are three other Indian cobra species), common krait (Bungarus caeruleus) (seven other krait species), Russell’s viper (Daboia russelii) and saw-scaled viper (Echis carinatus) [WHO 2010 Antivenom guidelines; Warrell, 2011; Warrell et al., 2013, Whitaker
The few studies from healthcare facilities found that antivenom treatment reduced deaths by over 90% (Appendix 2-table 1).

We estimate, crudely, that the in-hospital case-fatality rate based on the literature was about 3%. This in part reflects delay in reaching medical care, with only about half of the cases doing so within six hours. Public-private partnerships for ambulance services are possible. In some states, an emergency ambulance service equips vehicles with lifesaving equipment and drugs, including antivenom.

Ambulances can be summoned in 15 states of India by calling a toll free number [Gimkala et al., 2016]. In 2014, of 27,509 snakebite patients transported to hospitals within 6 hours, 359 patients died within 48 hours of follow-up. This represents a crude case-fatality rate of 1.3%, below the rate we estimate for in-hospital bites. This ambulance model is relevant to other parts of the country, especially the more remote areas in Bihar, Jharkhand and Odisha, which are not currently covered.

Finally, improved surveillance is required of venomous snake species as well as the human consequences of bites. An enhanced snake species database, hosted in collaboration with agricultural and forest departments, of their habitat details, clear photographs, and geographical distributions is now available as a downloadable Google app [Indian Snakes, 2019; WHO, 2019d]. There are at least 15 species of snake in India responsible for human deaths, and better information about them would aid control [Whitaker and Whitaker, 2006; Whitaker and Martin, 2015]. We show that public facility-based reporting of deaths captures only 10% of expected deaths in public and private hospitals. While much care in India occurs in private hospitals, disease reporting and surveillance by private facilities is likely to be similarly or even more deficient [Jha and Laxminarayan, 2009]. The Government of India could designate and enforce snakebite as a “Notifiable Disease” within the Integrated Disease Surveillance Program. However, since most deaths occur at home, community death tracking through the RGI’s ongoing mortality surveillance system will be needed. Both community and facility-based surveillance data are essential to better align interventions to prevent and treat snakebites to their heterogeneously distributed burden. For both hospital and community bites, it would be invaluable to document the circumstances and consequences of snakebites, including morbidity sequelae, with simple questions to investigate the circumstances of each bite or death/disability. This could include data such as use of boots, walking in the dark, sleeping patterns, and other questions. Similar investigative tools for HIV/AIDS have recently been proposed to add to the WHO’s standard verbal autopsy [Bogoch et al., 2018].

Limitations of our study

The major source of uncertainty in our estimates of snakebite deaths at national level arises not from random errors, as the MDS has a large sample size and the vital rates used as underlying denominators are reasonably complete [Menon et al., 2019], but from the misclassification of causes of death in the verbal autopsy. Earlier evaluations of the MDS showed strong reproducibility of the dual physician-
coded verbal autopsies, generally low rates of misclassification in children and young and middle-age adults, and high consistency with relevant hospital or clinical data [Gomes et al., 2017; Aleksandrowicz et al., 2014; Menon et al., 2019]. Moreover, two independent physicians agreed about 92% of the time on a diagnosis of snakebite deaths. Snakebite mortality may be under-estimated because the phenomenon of painless, unsuspected nocturnal krait (Bungarus) bites resulting in 'early morning paralysis' may not be attributed to snakebite [Saini et al., 1986; Ariaratnam et al., 2008], but this is likely to be a small bias. Our estimates for some states are uncertain due to small number of deaths recorded annually, which also prevented us from examining yearly spatial clustering patterns.

Our estimates of case-fatality rate and envenomations based on the systematic literature review has obvious limitations. First, the exact species of snake cannot be easily identified, and indeed, there are four species of cobra and eight species of kraits in the country [Whitaker and Captain 2004]. In addition, each species varies in the circumstances, seasonal and diurnal variation and types of terrain where bites most often occur. For example, anecdotal experience indicate that most bites from common kraits (Bungarus caeruleus) occur at night while people are sleeping on mats on the floor or ground, in or near home, unprotected by tucked-in mosquito nets [Ariaratnam et al., 2008; Kularatne, 2002; Bawaskar et al., 2002]. Most bites from saw-scaled vipers (Echis carinatus) happen either when the snake is stepped upon in bare or sandaled feet at night or when cutting grass by hand with a short sickle. Bites by cobras are divided into circumstances such as defensive bites while stepping on them during planting/harvesting crops, reaching into piles of straw or firewood and predatory bites when the cobra mistakes a human hand or foot for a prey item [Alirol et al., 2010]. Russell’s viper (D. russelii) bites occur during the day, inflicted on farmers in the paddy fields or while hand harvesting peanut plants, or at night when someone walks without using a light and steps on the snake [Whitaker and Captain 2004].

Another major uncertainty from the literature review are in the hospital-based data, given expected problems with publication biases and in the differences between patients seeking or not seeking hospital care. For example, serious cases are more likely to be hospitalized, raising the observed case-fatality rate. However, under various scenarios, our report of 20 to 40 bites per death is greater than the crude estimate of 20 envenomations per death we made earlier [Mohapatra et al., 2011]. Additional hospital-based surveillance, including tracking the severity of treated cases, could further refine the actual ratio of envenomations to deaths. These uncertainties demand appropriate caution in interpreting our basic estimate of the number of envenomations.

Conclusion
We conclude that snakebite deaths in India are concentrated largely within limited geographical areas, and involve particular communities during specific seasons. Our identification of the focused geographic and temporal spread of snakebites allows targeted prevention and treatment strategies.
that could help India to achieve the WHO’s goal of halving snakebite death and morbidity rates by 2030. Further use of large-scale epidemiological studies will be essential to review the success of such control programs.
METHODS

Data sources

To derive comprehensive and up-to-date estimates of snakebite mortality and prevalence, we collected all possible statistics related to snakebites in India from 2000 to 2015. The main data sources for this study were snakebite mortality data from the Indian Million Death Study (MDS), a systematic review of studies published in the scientific literature, and chronological statistics published by the Ministry of Health and Family Welfare of the Government of India.

Nationally representative mortality data

The methods, strengths, and limitations of the MDS and key results for various diseases have been extensively reviewed and published [Gomes et al., 2017, Aleksandrowicz et al., 2014, Menon et al., 2019]. Briefly, in collaboration with the Registrar General of India, the MDS monitored approximately 23 million people in 3.6 million nationally representative households in India from 1998 to 2014. The Registrar General of India’s Sample Registration System (SRS) established three sampling frames for the MDS, which covered years 1993-2003, 2004-13, and 2014-2023. The SRS randomly selects sampling units based on the 1991, 2001, and 2011 censuses for the respective sampling frames [Registrar General of India, 2017]. Mortality data used in this study were from 2001-3, 2004-13, and 2014, generated from these sampling frames. Semi-annually, about 900 non-medical surveyors recorded the details of each death that occurred in these households during the preceding six months using a well-validated verbal autopsy instrument (based on the 2012 WHO instrument and including a half-page local language narrative). Each record is converted to an electronic form and randomly assigned to two of 404 trained physicians, who each assign a cause of death using ICD-10 codes. Disagreements in assignment undergo anonymous reconciliation, and persisting differences undergo adjudication by a third physician. We included 2,833 snakebite deaths in our study by carefully examining 3,020 probable snakebite deaths that either of the two physicians had coded as X20 (venomous snakes), X27 (venomous animals) or X29 (not specific). We followed the same inclusion/exclusion method described in our earlier analyses [Mohapatra et al., 2011]. Out of the 3,020 possible snakebite deaths, there were 2,779 (92%) deaths in which both coders initially coded to X20. Review of these yielded no misclassified deaths. Re-examination of the symptoms and physician keywords for 105 deaths that one coder had coded as X20 and other coder as X27 or X29 revealed that 54 (2%) were snakebite deaths. No misclassified deaths were found in the 136 deaths that one coder had coded X20, X27 or X29 and the other coder had assigned a different ICD-10 code.

Statistical methods

Geospatial mapping of deaths

The SRS provided population data for the sampling units for 2004-13 [Registrar General of India, 2017]. These population values were partitioned into single-year ages by applying Census of India 2011 district-level single-year age structure proportions (by sex and rural/urban setting). District codes from
Census of India 2011 were converted to 2001 codes prior to linking with sampling units given that the 2004-13 sampling frame used 2001 codes. Sampling units that belonged to districts that split in 2011 used 2001 district codes from the parent districts. All sampling units that belonged to the same district, rural/urban setting and sex shared the same age structure proportions. We further linked the MDS data to these population data at the sampling unit level. Statistical analyses were based on data from 7,377 geocoded sampling units (out of 7,597 sampling units), after exclusion of sampling units from the islands.

We derived the spatially-smoothed absolute risks of snakebite mortality in India for 2004-13. First, using mortality data of ages 0-69 years (by five year age group) as the outcome and sampling unit population of the same age range as the offset, we fitted a Bayesian Poisson model to obtain the age- and sex-specific snakebite death rates at the national level. We did not include an intercept in the model, but included age-sex interaction term and time trend (using year 2010 as the reference value) as covariates. This formulation allowed us to obtain the estimated age- and sex-specific national death rates for year 2010. We then used a geostatistical Bayesian Poisson model to estimate the spatially-smoothed relative risks of snakebite mortality, by comparing the observed snakebite death rates at each sampling unit versus the national death rate (see Appendix 3 for details). The geostatistical models adjusted for time trends, urban/rural status, female illiteracy in rural areas, altitude, and average of long-term monthly mean temperature. We adjusted for urban/rural status of the sampling unit due to the higher risks of snakebite in rural areas compared to urban areas [Chaves, 2015]. We included female illiteracy in rural areas as a proxy of poverty effects on snakebite mortality, since the poor have higher risk of snakebite [Harrison, 2009]. We used sub-district-level female illiteracy data from the 2011 Indian census [Census of India, 2011]. We included altitude and long-term monthly temperature as covariates since they affect the occurrence of snakebite [Chaves, 2015]. Altitude data came from the NASA Shuttle Radar Topographic Mission’s digital elevation data version 4 [Jarvis, 2008]. Long-term monthly mean temperature came from the University of Delaware’s air temperature gridded dataset V5.01, with a 0.5 degree latitude/longitude grid resolution [Willmott and Matsuura, 2001]. We also included spatial random effects and sampling unit-level random effects in the model. Thus, the spatially-smoothed relative risks were the predicted relative risks of snakebite mortality across India. These relative risks were assigned to grid cells that covered the country (see Appendix 3: statistical supplement). Finally, we calculated the absolute risks of snakebite mortality across India by multiplying the spatially-smoothed relative risks (in each grid cell) by the national risks of dying before age 70 years from Table 1. National risks of dying used the average of annual risks of dying for 2004-13. The absolute risks represent the risk of dying from snakebite before age 70 years at the grid cell location. Population estimates in high risk areas were obtained by overlaying the absolute risk surface on the Gridded Population of the World version 4 for year 2015 [CIESIN, 2015]. Further technical explanation on the geostatistical Bayesian model is published [Brown, 2015]. Appendix 3 provides the model form, equations and implementation.
We performed a systematic review of snakebite studies in India. We searched the literature using a combination of keywords related to the study setting, metrics, treatment, snake species, and geography in Ovid MEDLINE(R), PubMed, Web of Science, and Scopus electronic databases. We selected relevant studies published in the English language from January 1 2000 to September 1 2019, to collect data for understanding case-fatality patterns and important snakebite characteristics in India. In addition, we hand searched articles that had cited our 2011 publication [Mohapatra et al., 2011]. Appendix 2 provides the keywords and inclusion and exclusion criteria. The search initially found 1,417 snakebite mortality and morbidity studies. After a careful review of titles, abstracts and quality of the studies by three independent reviewers (MB, KP and WS), 78 of the 95 possible studies were included in our analysis. We categorized the 78 studies to four study types: autopsy (seven studies: only deaths), emergency medical services (EMS) (one study of prevalence), hospital (66 studies: both prevalence and deaths) and community (four studies: both prevalence and deaths).

Mortality rates
We applied the SRS probability of selection sampling weights to the snakebite death frequencies to address urban and rural differences. We calculated snakebite mortality fractions using three-year backward moving averages of weighted snakebite death frequencies for each age, sex, and urban/rural stratum for each state of India. We interpolated the mortality fractions, using standard statistical methods for strata with zero death count [SAS Inc, 2014]. We applied these mortality fractions to SRS and the India census demographic framework to obtain the snakebite death rates. We then adjusted the death rates (usually upward by slight amounts) to the United Nations Population Division (UNPD) estimated India death totals [United Nations, 2019] to obtain the numbers of national and sub-national snakebite deaths. To address the remaining noise from crude death rates, we fitted cubic spline regressions to 2003 to 2014 cause-specific death rates while adjusting snakebite mortality to other causes of death to obtain the final estimates. We obtained estimates for the beginning and end of the period, including years 2001 and 2002 where data used for moving averages were less than three years, by extrapolating the spline curves to cover the overall period of 2000-2015. For comparison of rates across the years, we standardized the death rates to the 2001 census population. We calculated the number of in-hospital and out-of-hospital deaths by multiplying estimated deaths by percentages of study deaths that occurred in-hospital and out-of-hospital, as reported in the MDS. Appendix 1-figure 1 shows the data sources, data inputs and outcomes.

Snakebite prevalence estimates
We used an indirect method to estimate snakebite prevalence (which given very short duration of each bite effectively represents incidence) measured in terms of in-hospital and out-of-hospital prevalences.
This involved using the estimated MDS hospital deaths divided by case-fatality rate from systematic review of the literature to estimate the in-hospital prevalence and apply a hypothetical relationship between in-hospital and out-of-hospital prevalence to estimate the out-of-hospital prevalence. This is, by necessity, crude but provides some reasonable ranges to estimate the numbers of bites and envenomations in India in recent years. We applied all such prevalence estimates for 2015, as that was the closest year to the last MDS round of 2014. Appendix 1-table 2 provides details of the calculation and the assumptions.
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| Year | Study deaths from snakebite/all causes | Standardized death rate /100,000 (all ages) and age-specific rates /100,000 | Snakebite mortality risk | Estimated national deaths (000) |
|------|--------------------------------------|-------------------------------------------------|------------------------|-----------------------------|
|      |                                      | All ages      | 0-14  | 15-29 | 30-69 |                       |                        |
| 2001 | 199 /41826                           | 5.3           | 5.4   | 3.6   | 5.9   | 0.40%                  | 55.0                   |
| 2002 | 183 /41740                           | 5.2           | 5.2   | 3.5   | 5.8   | 0.39%                  | 55.3                   |
| 2003 | 179 /38798                           | 5.1           | 5.0   | 3.4   | 5.8   | 0.38%                  | 55.8                   |
| 2004 | 190 /37380                           | 5.0           | 4.6   | 3.5   | 5.7   | 0.38%                  | 55.6                   |
| 2005 | 244 /46755                           | 4.9           | 4.8   | 3.4   | 6.4   | 0.40%                  | 60.8                   |
| 2006 | 214 /47471                           | 5.3           | 4.7   | 3.2   | 6.7   | 0.40%                  | 62.7                   |
| 2007 | 225 /48536                           | 5.3           | 4.5   | 3.0   | 6.4   | 0.39%                  | 61.0                   |
| 2008 | 215 /47673                           | 5.1           | 4.2   | 2.8   | 5.9   | 0.36%                  | 57.4                   |
| 2009 | 183 /47873                           | 4.7           | 3.9   | 2.6   | 5.3   | 0.33%                  | 53.8                   |
| 2010 | 200 /45719                           | 4.3           | 3.9   | 2.6   | 5.0   | 0.32%                  | 52.4                   |
| 2011 | 185 /46099                           | 4.2           | 4.0   | 2.7   | 5.1   | 0.33%                  | 54.9                   |
| 2012 | 227 /46635                           | 4.3           | 4.3   | 2.8   | 5.4   | 0.36%                  | 59.2                   |
| 2013 | 214 /45331                           | 4.6           | 4.4   | 3.0   | 5.8   | 0.38%                  | 62.3                   |
| 2014 | 175 /29647                           | 4.7           | 4.2   | 3.0   | 5.9   | 0.37%                  | 61.2                   |
| 2001-2014 | 2833 /611483 | 4.8           | 4.5   | 3.1   | 5.8   | 0.37%                  | 807.5                  |

Plausible range (Lower, Upper) = (4.4, 5.0), (4.1, 4.7), (2.8, 3.2), (5.3, 6.0), (0.34%, 0.38%), (738.2, 833.4)

1 Death rates were standardized to the Indian population in census year 2001 to take into account minor changes in the age distribution over time.
2 The probability of dying due to snakebite before reaching age 70 years in the hypothetical absence of other competing causes of death. This was calculated by summing the 5-yearly standardized death rates from ages 0-69 years.
3 Total death estimates at all ages were calculated by applying the MDS sample weighted proportion of deaths from snakebites, using weighted 3-yearly moving average, to the United Nations Population Division (2017) death totals.
4 Plausible ranges: The inherent variation in these estimates is not from the underlying demographic estimates but in the determination of primary causes of death. Therefore, we used plausible ranges based on independent cause assignment by two physicians and subsequent agreement on ICD-10 codes (X20 or X29). The lower bound was based on immediate agreement of both physicians and upper bound based on either of two physicians coding snakebite deaths.
Table 2 – Estimated snakebite deaths in thousands by age and sex from 2000-2019 in India

| Age range        | Male (LL, UL) | Female (LL, UL) | Both (LL, UL) |
|------------------|---------------|-----------------|---------------|
| 0-14 years       | 149 (134, 154)| 176 (160, 180)  | 325 (294, 334) |
| 15-29 years      | 109 (102, 111)| 88 (82, 89)     | 197 (184, 199) |
| 30-69 years      | 290 (269, 303)| 253 (232, 260)  | 543 (501, 564) |
| 70 years or above| 54 (45, 60)   | 48 (44, 50)     | 102 (89, 110)  |
| All Ages         | 602 (551, 626)| 565 (518, 578)  | 1,167 (1068, 1204) |

1. Total deaths for 2001-2014 MDS study period were 807,500 (Table 1). Deaths for 2000-2019 were calculated by extrapolating these annual deaths. The extrapolated annual deaths in thousands for outside the study period were 54.0 for 2000, 62.3 for 2015, 62.0 for 2016, 61.4 for 2017, 60.3 for 2018 and 59.8 for 2019.

2. Lower limit (LL) and Upper limit (UL) are lower and upper uncertainty bounds for estimates. The major uncertainty in our analyses, however, is not the demographic totals, but the cause of death classification. Hence, the lower bound was based on immediate agreement of both physicians on the ICD-10 code for snakebite and upper bound based on either of two physicians coding as snakebite death.
### Table 3 - Snakebite death rates by state in India for 2001-2014

| State                  | Study Deaths in MDS | Annual average standardized death rate /100,000 | Estimated deaths for 2001-14 (000) |
|------------------------|---------------------|-----------------------------------------------|----------------------------------|
|                        | 2001-2004 | 2005-2009 | 2010-2014 | Trend |
| **Higher burden states** |            |            |           |       |
| Andhra Pradesh         | 271       | 8.5       | 7.3       | 5.6   | 82.9 |
| Bihar                  | 321       | 5.6       | 7.6       | 8.9   | 101.9 |
| Odisha                 | 191       | 7.5       | 7.2       | 5.9   | 40.3 |
| Madhya Pradesh         | 195       | 6.7       | 7.7       | 6.0   | 67.8 |
| Uttar Pradesh          | 322       | 5.2       | 5.9       | 6.0   | 153.6 |
| Rajasthan              | 192       | 4.9       | 6.7       | 5.0   | 52.1 |
| Gujarat                | 176       | 4.1       | 4.8       | 5.1   | 38.8 |
| Jharkhand              | 58        | 4.9       | 2.0       | 7.1   | 20.1 |
| **Lower burden states** |            |            |           |       |
| Chhattisgarh           | 42        | 6.0       | 6.5       | 2.5   | 16.8 |
| Jammu & Kashmir        | 64        | 5.3       | 7.0       | 0.9   | 7.0  |
| Tamil Nadu             | 176       | 6.1       | 3.4       | 3.0   | 42.1 |
| Karnataka              | 137       | 5.6       | 3.3       | 2.9   | 33.0 |
| Maharashtra            | 147       | 4.2       | 3.7       | 2.6   | 56.0 |
| West Bengal            | 188       | 4.1       | 3.3       | 2.9   | 42.7 |
| Punjab                 | 67        | 2.9       | 3.1       | 4.0   | 14.5 |
| Haryana                | 45        | 2.9       | 3.3       | 1.8   | 9.5  |
| Assam                  | 27        | 2.8       | 0.7       | 2.1   | 7.3  |
| Northeastern states    | 37        | 2.3       | 0.9       | 0.7   | 2.4  |
| Kerala                 | 43        | 1.8       | 1.3       | 0.5   | 6.5  |
| All other states       | 134       | 4.3       | 3.9       | 3.2   | 12.2 |
| **All India**          | 2833      | 5.1       | 4.9       | 4.5   | 807.5 |

States are in descending order of annual average death rates for the study period of 2001-2014. We included only the states with populations over 10 million. Andhra Pradesh included Telangana. The Northeastern states include Arunachal Pradesh, Manipur, Meghalaya, Mizoram, Nagaland, Sikkim and Tripura.
Table 4 - Government hospital reports of snakebites and deaths, compared to MDS death totals by state for 2003-2015

| State            | No. of bites (000) | No. of deaths (000) | % died in hospital | Total No. of deaths (000) | No. died in hospital (000) | % Government coverage |
|------------------|--------------------|---------------------|--------------------|---------------------------|----------------------------|-----------------------|
| Higher burden states |                    |                     |                    |                           |                            |                       |
| Andhra Pradesh   | 530.0              | 6.9                 | 19%                | 539.6                     | 94.6                       | 7%                    |
| Bihar            | 251.3              | 1.4                 | 16%                | 74.1                      | 11.6                       | 12%                   |
| Odisha           | 20.9               | 0.1                 | 16%                | 105.4                     | 17.0                       | 1%                    |
| Madhya Pradesh   | 76.2               | 1.8                 | 29%                | 36.9                      | 10.9                       | 17%                   |
| Uttar Pradesh    | 28.3               | 1.1                 | 22%                | 64.4                      | 14.1                       | 8%                    |
| Rajasthan        | 27.8               | 0.6                 | 13%                | 150.7                     | 20.2                       | 3%                    |
| Gujarat          | 71.3               | 1.0                 | 16%                | 49.6                      | 7.8                        | 13%                   |
| Jharkhand        | 45.7               | 0.8                 | 27%                | 38.6                      | 10.5                       | 7%                    |
| Percentage to national | 530.0          | 6.9                 | 19%                | 539.6                     | 94.6                       | 7%                    |
| Lower burden states |                  |                     |                    |                           |                            |                       |
| Chhattisgarh     | 277.2              | 8.6                 | 28%                | 219.8                     | 59.6                       | 14%                   |
| Jammu & Kashmir  | 16.7               | 0.3                 | 17%                | 14.3                      | 2.4                        | 13%                   |
| Tamil Nadu       | 18.4               | 0.0                 | 26%                | 5.9                       | 1.5                        | 2%                    |
| Karnataka        | 106.6              | 0.5                 | 28%                | 36.0                      | 10.0                       | 5%                    |
| Maharashtra      | 89.2               | 1.6                 | 21%                | 28.1                      | 6.0                        | 26%                   |
| West Bengal      | 178.7              | 1.2                 | 25%                | 49.0                      | 12.5                       | 10%                   |
| Punjab           | 208.9              | 3.4                 | 41%                | 38.9                      | 15.9                       | 22%                   |
| Haryana          | 9.1                | 0.2                 | 10%                | 14.2                      | 1.4                        | 13%                   |
| Assam            | 14.3               | 0.1                 | 16%                | 8.5                       | 1.3                        | 11%                   |
| Northeastern states | 3.6               | 0.1                 | 32%                | 6.6                       | 2.1                        | 3%                    |
| Kerala           | 11.1               | 0.1                 | 25%                | 1.8                       | 0.4                        | 11%                   |
| All other states | 37.9               | 0.2                 | 27%                | 5.2                       | 3.5                        | 6%                    |
| Percentage to national | 777.2          | 8.6                 | 28%                | 219.8                     | 59.6                       | 14%                   |

1 Government statistics are as published by the Ministry of Health and Family Welfare, Government of India [GOI, 2015]. 2 Higher burden states are those where the snakebite death rate at all ages is above 5/100,000 deaths for the entire study period of 2001-14 as listed in Table 3. In cases of number less than 100 deaths, they are listed as 0.0 in thousands.
Figure 1 – Spatial distribution of snakebite mortality risk in India for 2004-13

Note: About 0.33% of the Indian population lived in areas with an absolute risk of 1% or greater of dying from snakebite before age 70 years, and 21% lived in areas with absolute risk of 0.6% or higher. Population estimates used the Gridded Population of the World version 4 for year 2015 [CIESIN, 2015]. Further details of statistical method and stochastic uncertainties of spatial mortality risk pertaining to these estimates are explained in Appendix 3.
Figure 2 – Predicted daily snakebite deaths from analysis of seasonality observed in 2001-2014 (Panel A) and snakebite crude death rates by altitude in meters in 2004-13 (Panel B)

Notes: The daily snakebite totals are a composite of all study years from 2001-14. The crude death rates by elevation use the RGI’s Sample Registration System population as denominators, and hence are generally lower than the overall rates we apply to the whole of India (using the United Nations death totals, which has the benefit of taking into account undercounts in the SRS data [Menon et al., 2019]. However, the relationship of crude death rates with elevation is unaffected by this procedure.
Figure 3 – Characteristics of snakebites from analysis of 88,000 snakebite events in the published literature.
A

B

Crude death rate (per 100,000)

Elevation (m)
Crude death rate (per 100,000)
- No snakebites
- 0 - 10
- 10 - 30
- > 30
- No data available
Identified through database search (n = 1414)

Additional identified hand search (n = 3)

Total identified (n = 1417)

Duplicates removed (n = 15)

Screened (n = 1402)

Excluded (n = 1307)

1307 excluded:
(a) 520 secondary reviews and reports on trends in snake bite distribution, risk factors and management
(b) 334 animal or pharmacological studies on experimental drugs
(c) 200 studies on herbal therapies and other treatment strategies
(d) 20 studies beyond India or on other injuries or health conditions
(e) 231 biomedical/case studies describing only the biological mechanism and manifestations of a snake bite
(f) 2 conducted prior to 2000

Full-text articles assessed for eligibility (n = 95)

Studies included in systematic review (n = 78)

12 excluded were conference abstracts, which had no full-text copies available or full text articles that had not enough relevant data to extract for the purpose of this review. 5 other studies failed at quality assessment.
