

BMJ Open Animal-related injuries and fatalities: evidence from a large-scale population-based cross-sectional survey in rural Bangladesh

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ABSTRACT

Objective This study determines the magnitude and pattern of animal-related injury mortalities and morbidities in rural Bangladesh.

Design and setting A cross-sectional survey was conducted in 51 Unions of 7 subdistricts of Bangladesh from June 2013 to September 2013.

Participants A total of approximately 1.17 million individuals across all age and gender profiles were included in the survey. The participants had to be residents of the seven subdistricts and have provided consent to participate in the study.

Primary and secondary outcome measures Animal-related injury characteristics and demographic information was collected in the study. Frequency, proportion and 95% CIs of variables such as type of animal, type of animal attack, activity of the person prior to attack and the seasonality of the injury were reported. Data was then statistically analysed for associations between injury and sociodemographic characteristics.

Results The incidence rate of fatal and non-fatal animal-related injuries across all ages were 0.7 (95% CI 0.4 to 1.4) and 1635.3 (95% CI 1612.0 to 1658.0) per 100 000 populations, respectively. Non-fatal animal-related injury rates were highest among adults 18 years and older (1820.6 per 100 000 population (1777.2 to 1865.1)), and in males across all age groups. The most common animal injury was wasp/hornet/bee sting (49%), followed by cow/buffalo (25%), dog bite (9%) and snake bites (9%).

Conclusions Animal-related injuries are an important public health issue in rural Bangladesh. The incidence of animal-related morbidities was found high in the study area. Males, school-going and productive age groups were at high risk. Immediate attention should be given to prevent these events.

INTRODUCTION

Animal injuries are becoming an increasing public health issue among children and adults. Animal attacks cause a large number of injuries and deaths and lead to significant medical and social consequences worldwide.¹ About 50% of all individuals experience at least one animal bite in their lifetime, especially during childhood.² Animal injuries are

Strengths and limitations of this study

- The study was based on a large-scale population covering 1.17 million people and thus provides more accurate estimates of animal-related injury in rural Bangladesh.
- Even though animal-related injuries are locally and regionally variable, the findings from this study can be conservatively generalised to other parts of the country and other low- and middle-income countries with similar age group, gender and socioeconomic status distributions.
- The recall period for non-fatal injuries in this study was 6 months and reported rates have been annualised under the assumption that rates were consistent throughout the year — which is a major limitation of this study.
- The study was conducted in rural Bangladesh and findings might not be generalisable to urban parts of the country where exposure and risk factors vary.

most commonly due to but not limited to snakes, dogs, cats and monkeys, accounting for more than 55 000 deaths worldwide.³

The health impacts of an animal injury depend on the type and health of the animal, the size and health of the human victim and accessibility to treatment.^{3 4} Approximately 90% injuries are from domestic animals and 70% of those are from pets.^{2 5} Animal-related injuries can also be caused by butting, impaling or stepping on an animal.⁶ Apart from these types of animal attacks, snake bites are often associated with high mortality and morbidity and are considered to be an one of the most common occupational injuries among the poor and vulnerable rural people in South East Asia.⁷ Fatal anaphylactic reactions are also seen due to some stinging insects such as swarming social hornets, bees, ants, scorpions and wasps.^{4 8}

However, animal-related injuries have still not received much attention in low- and

middle-income countries.⁴ Bangladesh has the third highest mortality rate among rabies-endemic countries and children under 15 years of age from poor rural communities are affected the most.⁹ Snake bites are also a common health problem in Bangladesh's rural community, where the rate was 623.4/100 000 person years.¹⁰ In 2007, surveillance system of the Directorate General of Health Services found snake bite was the leading cause of mortality during flood disaster. Unlike other injuries, the exact burden of animal injuries in Bangladesh is quite difficult to estimate because of poor reporting systems and lack of population level data for both fatal and non-fatal animal injury events.^{7 9 10} Therefore, it is important to explore the present epidemiological status of animal-related injury mortalities and morbidities in Bangladesh to implement injury prevention programmes across the country. A subset of the sociodemographic and injury-related information collected as part of a drowning prevention project 'Saving of Lives from Drowning (SoLiD) in Bangladesh' was used to describe the epidemiology and associated risk factors of animal-related injuries in rural Bangladesh in this particular study.

METHODS

Study design, area and population

A baseline survey was conducted in 2013 to collect epidemiological information on fatal and non-fatal injuries, as part of a drowning prevention intervention study, SoLiD.^{11 12} The census was held in seven subdistricts (upazilas) of rural Bangladesh - Matlab North, Matlab South, Daudkandi, Chandpur Sadar, Raiganj, Sherpur Sadar and Monohardi and covered approximately 1.17 million people in 51 Unions from these selected areas. These subdistricts were chosen purposively as a higher rate of childhood drowning was found there.

Data collection tools and technique

Information was collected on fatal and non-fatal injury outcomes (including animal injuries) from household heads or adult respondents (above 18 years of age) by face-to-face interview using pretested structured questionnaires. Data collection was conducted in two stages.

In the first stage, general demographic information on all household members was collected along with history of any injury in the past 6 months and deaths in the past 1 year. Injury was operationalised as 'any external harm resulting from an assault, fall, cut, burn, animal injury, poisoning, transportation of goods and persons, operating machinery, blunt objects, suffocation and (near) drowning resulting in the loss of one or more days of normal daily activities, schools or work'. In the second stage of data collection, detailed information was obtained on any injury-related mortality and morbidity that was reported during the first round of data collection. Each specific injury mechanism had a specific module pertaining to relevant circumstances

(see online supplementary appendix). The methods have been described in detail elsewhere.¹³

Quality control of data

To maintain the quality of data, trained supervisors were appointed. Around 10% of interviews were re-observed that were conducted by the data collectors, 10% of the collected data were rechecked and 2% of the households were re-interviewed by the supervisors. All the data were rechecked for inconsistencies. Also, field managers and coordinators were asked to recheck the data for inconsistencies. For inconsistent data, the concerned data collector was asked to revisit that household to collect the correct information.

Patient and public involvement

During the development of the survey tools, measurements and the study protocol, several meetings were held with the local partners, government officials and researchers in Bangladesh to discuss the needs and gaps of the injury deaths and health survey planned for rural Bangladesh. The instruments were then modified according to the needs of the Bangladeshi population as recommended in the meeting. This study examined the participants (household head) in their home environment and did not enrol any clinical patients.

Statistical method and analyses

For the purposes of this paper, the analysis was restricted to all animal injury-related events from the baseline census. Descriptive statistical analyses were conducted for fatal and non-fatal animal-related injury outcomes and were estimated as counts, proportions and 95% CIs across sociodemographic factors such as age, gender, occupation, educational level and socioeconomic status. Injury characteristics such as the animal, injury type, activity of the person prior to attack and the seasonality of the animal-related injury were also calculated. Fatal and non-fatal animal-related injury rates were calculated per 100 000 population per year. Since the recall period for non-fatal injuries was 6 months, the rates were annualised by multiplying by a factor of 2 under the assumption that the rate was consistent throughout the year.

Determinants of non-fatal animal-related injury outcomes were modelled as ORs comparing levels of independent variables using logistic regressions. The variables age, gender, occupation, education level, socioeconomic status, marital status and subdistrict were included as variables in the regression model. As these variables are known risk factors for animal injury from past research, all variables were included in the final multivariable regression model. Results from both bivariable and multivariable analyses are presented. Associations were not compared for fatal injury events as only eight deaths were recorded. Results were considered significant at a p value of less than 0.05.

A population-level injury severity index was developed based on indicators like anatomical and physiological profiles of an injury, post-injury immobility, post-injury hospitalisation, surgical treatment, post-injury disability, number of days an individual required assistance and the number of days lost at work or school — information collected as part of the baseline census.¹⁴ A linear combination of a set of variables were accounted for to come up with a custom index of severity. The injury severity indices for all non-fatal injuries were calculated and segregated into tertiles of low, medium and high severity. All analyses were conducted on Stata quantitative analysis software (StataCorp 15.1).

RESULTS

In the SoLiD baseline survey, a total population of approximately 1.17 million people were studied across the seven subdistricts of Bangladesh. (table 1) Overall, the majority population was females (51.5%, n=601 919), 18 years of age and above years of age (60%), had no education or received at least primary level education (60%), were married (49%, n=576 352), unemployed (78%) and were either retired, unemployed or housewives (35%, n=408 583). Around 30% (353 531) had received secondary and higher education. The respondents by subdistrict was Matlab North (22.7%), Matlab South (18%), Chandpur Sadar (11%) of Chandpur district, Sherpur Sadar (19.5%) of Sherpur district, Monohardi (17.5%) of Narsingdi district and Raiganj (8.9%) of Sirajganj district. Detailed characteristics of the sample population have also been described in previous work.¹³

Characteristics of fatal and non-fatal animal-related injury

A total of eight fatal animal-related injury events were recorded in this census, and the mortality rate in this population was 0.7 per 100 000 population (95% CI 0.4 to 1.4). Animal-related injury mortality rates were predominantly seen in males and were higher than deaths in females. Children 1 to 5 years of age had the highest rates of fatal animal injuries 1.1 per 100 000 population (95% CI 0.2 to 6.3). Mortality rates were also higher among those who did not receive any formal education, involved in agriculture, never-married and the lowest wealth quantile. Mortality rates were highest in the Sherpur subdistrict among all subdistricts surveyed (1.3 per 100 000 population) (table 1).

There were 9563 animal-related incidents among the population surveyed, with the morbidity rate of 1635.3 injuries per 100 000 population (95% CI 1612.0 to 1658.0). The frequency of non-fatal animal-related injuries rates was highest among males 1837.3 per 100 000 population (95% CI 1803.0 to 1873.0), and among the people 18 years and older 1820.6 per 100 000 population (95% CI 1777.2 to 1865.1). Rates of non-fatal animal-related injuries were higher among those with no formal education 1132.4 per 100 000 populations (95% CI 1095.0 to 1171.0), in those who practiced agriculture, among the

married and in the low socioeconomic status (SES) quintile (table 1). The highest non-fatal animal-related injury rates were seen in Raiganj at 2648.6 per 100 000 populations (95% CI 2553.0 to 2748.0), followed by Monohardi and Sherpur upazilas.

Most non-fatal animal injuries occurred in the monsoon season, with a peak between June and August (figure 1).

Over 65% of the animal-related injuries occurred without any provocation and 67% of injuries occurred by stinging. The highest proportion of animal injuries was caused by the hornets/wasps/bees (51%), followed by cow/buffalo (25%) (figure 2).

Most non-fatal animal-related injuries had low severity (81.6%) and only 6.1% cases were severely injured (table 2).

Determinants of regression for non-fatal animal-related injury outcomes

Females had 30% lower odds of animal injuries compared with males (OR 0.7, 95% CI 0.6 to 0.7) (table 3). Children and adults 18 years and above were at highest risk of animal-associated injuries compared with all other age groups (OR 0.2, 95% CI 0.1 to 0.3; OR 0.8, 95% CI 0.6 to 0.9 and OR 1.1, 95% CI 0.9 to 1.3) (table 3). Higher education was associated with lower odds of animal-related injuries. People with secondary education had 20% lesser odds of having animal-related injuries than those with no education (OR 0.8, 95% CI 0.7 to 0.9) (table 3). People involved in agriculture had the highest odds of animal-related injuries than any other occupations. SES had an inverse relationship with odds of animal-related injuries, higher the SES, lower the odds of having an animal sting related injury. Raiganj had a 3.6 times (95% CI 3.44 to 3.9) higher risk of having animal stings among its residents when compared with Matlab North.

DISCUSSION

Animal-related injuries are an important cause of morbidity and a major public health concern in Bangladesh. In our study, animal-related injuries were common in rural Bangladesh, with a morbidity rate of 1635.3 injuries per 100 000 populations. Most of the animal-related injuries were caused by hornets/wasps/bees stings (67%). Males were at higher odds of having animal-related injuries than females. Animal-related injuries were more common in children and the working population, mainly among those involved in agriculture. Education and SES had an inverse relationship with the odds of having animal injuries. In addition, more than 72% injuries occurred during the rainy season. More than 35% injuries occurred by provoking the animal or during feeding/using for work. More than 81% victims did not require hospitalisation.

Increased risk among males compared with the females has been previously reported by the WHO and in other

**Table 1** Fatal and non-fatal animal-related injury rates (per 100 000) by sociodemographic characteristics

Characteristics/variables	Total population (N %)	Fatal animal-related injury (n=8)		Non-fatal animal-related injury (n=9563)	
		n=8	Rate/100 000/year (95% CI)	n=9563	Rate/100 000/year (95% CI)
Sex					
Male	567 674 (48.5)	5	0.9 (0.4 to 2.1)	5215	1837.3 (1803.0 to 1873.0)
Female	601 919 (51.5)	3	0.5 (0.2 to 1.5)	4348	1444.7 (1415.0 to 1475.0)
Age group					
<1 years	22 141 (1.9)	–	–	20	92.6 (59.8 to 143.5)
1–5 years	90 523 (7.7)	1	1.1 (0.2 to 6.3)	387	843.6 (763.9 to 931.9)
5–17 years	343 947 (29.4)	3	0.8 (0.3 to 2.6)	2619	1510.3 (1453.8 to 1569.1)
18 years and above	712 982 (60.9)	4	0.6 (0.2 to 1.4)	6537	1820.6 (1777.2 to 1865.1)
Level of education					
No education	295 314 (25.3)	4	1.4 (0.5 to 3.5)	3344	1132.4 (1095.0 to 1171.0)
Primary	407 923 (34.9)	4	1.0 (0.4 to 2.5)	3701	907.3 (878.6 to 936.8)
Secondary and above	353 531 (30.2)	–	–	2110	1048.7 (1001.9 to 1097.3)
Not applicable (U5 children)	112 664 (9.6)	1	0.9 (0.2 to 5.0)	407	361.3 (327.5 to 398.5)
Occupation					
Agriculture	104 956 (9.0)	2	1.9 (0.5 to 6.9)	1642	1564.5 (1491.0 to 1641.0)
Business	61 661 (5.3)	–	–	529	857.92 (788.1 to 933.8)
Skilled labour (professional)	89 151 (7.6)	–	–	494	554.1 (507.5 to 605.0)
Unskilled/domestic (unskilled)	24 520 (2.1)	–	–	227	925.8 (813.4 to 1054.0)
Rickshaw/bus (transport worker)	17 037 (1.5)	–	–	120	704.4 (589.4 to 841.5)
Students	312 537 (26.7)	2	0.6 (0.2 to 2.3)	2344	749.8 (720.3 to 780.8)
Retired/unemployed/ housewife	408 583 (35.0)	1	0.2 (0.04 to 1.4)	3518	861.0 (833.2 to 889.8)
Children	144 454 (12.4)	1	0.7 (0.1 to 4.0)	621	429.9 (397.5 to 465.0)
Others	5948 (0.5)	2	33.6 (9.2 to 122.5)	65	1092.8 (858.4 to 1390.0)

U5, under-five.

Marital status	Total population (N %)	Fatal animal-related injury (n=08)		Non-fatal animal-related injury (n=9563)	
		n=8	Rate/100 000/year (95% CI)	n=8	Rate/100 000/year (95% CI)
Married	5 671 206 (48.8)	4	0.7 (0.3 to 1.8)	5624	984.6 (959.3 to 1011.0)

Continued

Table 1 Continued

Marital status	Total population (N %)	Fatal animal-related injury (n=08)		Non-fatal animal-related injury (n=9563)	
		n=8	Rate/100 000/year (95% CI)	n=8	
Never-married	227 319 (19.4)	2	0.9 (0.2 to 3.2)	1261	554.7 (525.0 to 586.1)
Widowed/divorced/separated	59 033 (5.1)	–	–	531	899.5 (826.5 to 978.9)
Children (<12 years)	312.035 (26.7)	2	0.6 (0.2 to 2.3)	2147	688.1 (659.7 to 717.7)
Wealth quantile					
Lowest	211 601 (18.1)	3	1.4 (0.5 to 4.2)	2019	954.2 (913.6 to 996.5)
Low	218 695 (18.7)	2	0.9 (0.3 to 3.3)	2136	976.7 (936.3 to 1019.0)
Middle	238 371 (20.4)	1	0.4 (0.1 to 2.4)	1857	779.0 (744.5 to 815.1)
High	247 716 (21.2)	2	0.8 (0.2 to 2.9)	1943	784.4 (750.4 to 819.9)
Highest	253 210 (21.7)	–	–	1608	635.1 (604.8 to 666.7)
Subdistrict					
Matlab North	265 897 (22.7)	2	0.8 (0.2 to 2.7)	1849	695.4 (664.5 to 727.7)
Matlab South	209 772 (18.0)	–	–	1134	540.6 (510.1 to 572.9)
Chandpur Sadar	128 356 (11.0)	–	–	259	201.8 (178.7 to 227.9)
Raiganj	104 357 (8.9)	1	1.0 (0.2 to 5.4)	2764	2648.6 (2553.0 to 2748.0)
Sherpur	228 519 (19.5)	3	1.3 (0.5 to 3.9)	1697	742.6 (708.2 to 778.6)
Monohardi	204 319 (17.5)	2	1.0 (0.3 to 3.6)	1695	829.6 (791.2 to 869.8)
Daudkandi	28 373 (2.4)	–	–	165	581.5 (499.5 to 676.9)

studies.^{3 15–17} Males are predominantly involved in agriculture in rural Bangladesh which increases their exposure to animals and insects in the physical environment.

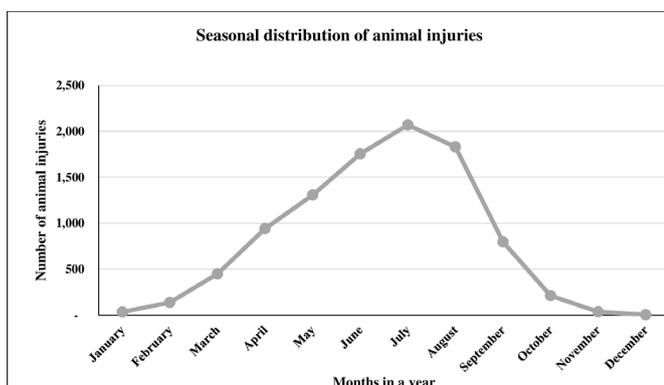


Figure 1 Non-fatal animal injuries over a 1 year period.

Additionally, younger men exhibit risk taking behaviour, which might entail provoking an animal.^{3 4} Rice, jute and tea are common agricultural produce in rural Bangladesh and attract rodents, which are prey for snakes and other non-domesticated animals.^{7 18–21} During farming, animal-related injury is a major occupational injury in the USA and other high-income countries and lack of knowledge has been identified as one of the key reasons.^{22–25} Severe injuries and even deaths may occur from large animals, such as horses, bulls and swine. In addition to farmers, other occupations such as veterinarians, cowboys, animal caretakers, pet store operators and even researchers are at risk of trauma or zoonotic infections due to the nature of their work.^{22–25}

As seen in this study, past studies have shown that the adult population above 18 years of age is most commonly affected by animal injuries — the most economically

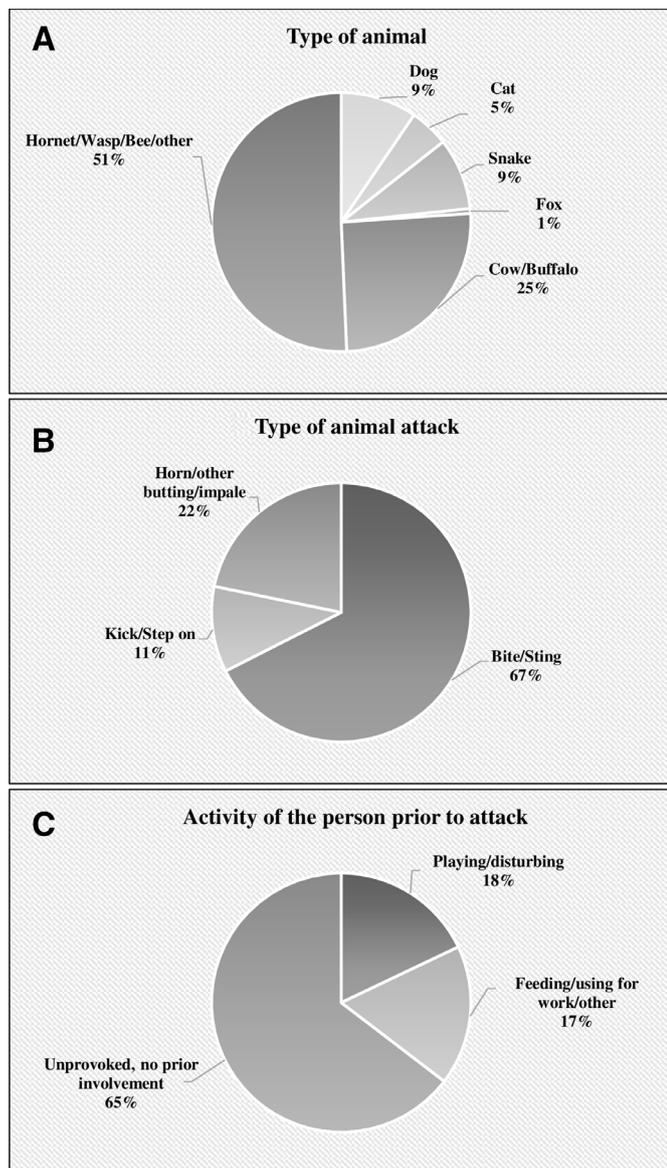


Figure 2 Factors associated with fatal and non-fatal animal injuries: (a) types of animals that caused an injury, (b) type of animal attack, (c) activity of the person prior to animal attack.

active group of the society that is also most exposed to hazardous environmental and occupational injuries.^{4 26–28} Another study found that individuals with no or little education are at higher risk for animal-related injury — similar to results seen in our study.²² Contrary to these findings, one hospital-based study reported peak age of incidence of dog bites among children 15 years of age and below.⁹ Young children can be exposed to street dogs

Table 2 Injury severity index for non-fatal animal-related injuries

Injury severity	N	Frequency (%)
Low	7801	81.6
Medium	1183	12.4
High	579	6.1

during play hours thus increasing their risk of animal injury.

Most of the non-fatal animal-related injuries occurred typically in the rainy season as venomous animals mostly appear around this time of the year.²³ According to Wide-Ranging Online Data for Epidemiologic Research database, USA, most of the fatalities occur as a result of unexpected injury by the farm animals, bees, wasps or hornet stings, and dog attacks also.²⁴ This study shows the highest rate (51%) of animal-related injuries by the hornets/wasps/bees sting. On the other hand, few studies have also identified insect stings as a potential cause of animal-related injury.^{3 9 22–24} WHO reports highest occurrence (76% to 94%) of dog bites is in low- and middle-income countries (LMICs) and Bangladesh is ranked third among countries where rabies is endemic. Playing, feeding and provoked activities are recognised as common prior activities in this study and related results were found in other studies.^{1 25 29}

Most injury epidemiology studies are based on facility-based surveillance data. The strength of our study is a large population-based sample size of about 1.17 million people providing stronger estimates on the prevalence of animal injuries in Bangladesh. Yet, this study also has some limitations. We cannot generalise the results to the entire country as the study was conducted in rural settings of Bangladesh only and the risk factors for urban settings might vary. However, our study findings may be generalisable to similar settings in other LMICs. In addition, the non-fatal animal-related injury rates may be under-reported due to challenges in data collection, recall and selection (purposely selected) bias,¹¹ stigmatisation and for family punitive reasons (especially children and adolescent group) or to accompany the census data collection. Additionally, the lack of year-round statistics on the burden of animal-related injuries introduces bias in the findings of this study and should be interpreted with caution when considering the seasonal variations of animal-related injuries.

This study suggests that the prevalence of animal-related morbidities was high in rural areas, posing a serious public health problem in Bangladesh especially among the high-risk individuals such as males, school and productive age groups, and individuals from lower socioeconomic status. Findings also suggest that, animal-related injury linked to agriculture is a major occupational hazard in rural Bangladesh, and injury from unsafe interactions with domesticated animals is a major risk for young children. Strategies like education programmes to educate farmers in first aid, or encouraging parents to use cots and nets for their children that have already helped to reduce animal-related injuries in other LMICs can be developed for preventing animal-related injuries in Bangladesh.³⁰ Implementation research on community awareness may support the development of a national strategy. We need further research to identify and accurately describe the actual burden of animal-related injuries on a national level

Table 3 Unadjusted and adjusted analysis of non-fatal animal-related injury by age group, sex, education, occupation, marital status and socioeconomic status quintiles

Characteristics/variables	Non-fatal animal-related injury			
	OR unadjusted	95% CI	OR adjusted	95% CI
Sex				
Male	Reference		Reference	
Female	0.8	0.7 to 0.8	0.7	0.6 to 0.7
Age group				
<1 year	0.1	0.1 to 0.2	0.2	0.1 to 0.3
1–4 year	0.5	0.4 to 0.5	0.8	0.6 to 0.9
5–17 year	0.9	0.8 to 0.9	1.1	0.9 to 1.3
18 years and above	Reference		Reference	
Level of education				
No education	Reference		Reference	
Primary	0.8	0.7 to 0.8	1	0.9 to 1.1
Secondary and above	0.5	0.4 to 0.6	0.8	0.7 to 0.9
Not applicable (U5 children)	0.3	0.2 to 0.4	(omitted)	
Occupation				
Agriculture	Reference		Reference	
Business	0.5	0.4 to 0.6	0.7	0.6 to 0.8
Skilled labour (professional)	0.3	0.3 to 0.4	0.5	0.4 to 0.5
Unskilled/domestic (unskilled)	0.8	0.5 to 0.8	0.8	0.7 to 0.9
Rickshaw/bus (transport worker)	0.4	0.3 to 0.5	0.5	0.4 to 0.6
Students	0.5	0.4 to 0.5	0.9	0.8 to 1.0
Retired/unemployed/ housewife	0.6	0.5 to 0.6	0.9	0.8 to 1.0
Children	0.3	0.2 to 0.3	0.7	0.6 to 0.8
Others	0.7	0.5 to 0.9	0.8	0.6 to 1.0
Marital status				
Married	Reference		Reference	
Never married	0.5	0.5 to 0.6	0.5	0.5 to 0.6
Widowed/divorced/separated	0.9	0.8 to 1.0	1	0.9 to 1.1
Children (<12 years)	0.7	0.6 to 0.7	0.7	0.6 to 0.8
Wealth quantile				
Lowest	Reference		Reference	
Low	1	0.9 to 1.1	1	0.9 to 1.1
Middle	0.8	0.7 to 0.9	0.9	0.9 to 1.1
High	0.8	0.7 to 0.9	1	0.9 to 1.1
Highest	0.7	0.6 to 0.7	0.9	0.8 to 1.0
Subdistrict				
Matlab North	Reference		Reference	
Matlab South	0.8	0.7 to 0.8	0.7	0.7 to 0.9
Chandpur Sadar	0.3	0.2 to 0.4	0.3	0.2 to 0.3
Raiganj	3.9	3.6 to 4.1	3.6	3.4 to 3.9
Sherpur	1.1	1.0 to 1.2	1	0.9 to 1.1
Monohardi	1.2	1.1 to 1.3	1.2	1.1 to 1.3
Daudkandi	0.8	0.7 to 0.9	0.8	0.7 to 0.9

U5, under-five.

and to establish and implement effective animal-related injury prevention programmes across the country.

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Contributors AAB, OA, AR and PA conceived the paper, contributed to the data analysis and reviewed the final draft for intellectual content. AAB wrote the initial drafts of the manuscript. PA contributed to the data analysis and reviewed multiple drafts of the manuscript for intellectual content. SW, QL and FR reviewed the final draft of the manuscript for intellectual content. All co-authors provided editing support in finalising the manuscript. In addition, we would like to thank Eric Schulman, Communications Specialist of Johns Hopkins International Injury Research Unit for assistance with English language editing.

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Competing interests None declared.

Patient consent for publication Not required.

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Data availability statement Data are available in a public, open access repository. Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

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