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# Visceral leishmaniasis associated mortality in Bangladesh: A retrospective cross-sectional study

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## Abstract

**Objective:** To investigate the actual visceral leishmaniasis mortality and its risk factors in the endemic regions in Bangladesh

**Design:** Retrospective cross sectional

**Setting:** Two geographically and culturally different visceral leishmaniasis endemic sub-districts, Godagarai under Rajshahi District and Trishal under Mymensingh District in Bangladesh, August 2009 – December, 2011

**Participants:** 51094 inhabitants from randomly selected two Unions in the two sub-districts.

**Main outcome measures:** Death by visceral leishmaniasis as reported by the family members was confirmed by three expert physicians independently by using Verbal Autopsy procedure ICD10 guideline.

**Results:** A total of 12032 households were studied, with a population of 51094 inhabitants, where 26160 inhabitants (6566 households) were from the Rishikul Union under Godagari Subdistrict, Rajshahi. Average age of the study population was 25.6 years (SD, 18.4) and 49.7% were female population. Case fatality rate was about 1.5% (2/137) in Mymensingh whereas it was about 17.0 % (10/59) in Rajshahi. Visceral leishmaniasis case fatality rate in the Tribal ethnic (22.2%) population was about 17 times higher than the Bangali ethnic (1.3%) population ( $P<0.0001$ ). About 75% (9/12) visceral leishmaniasis diseased died at home. The households with Tribal-ethnicity was 18 times ( $OR=18.1$ , 95% CI, 3.6-90.6) higher risk of getting visceral leishmaniasis death than the households with Bangali ethnicity ( $P<0.0001$ ).

**Conclusion:** Visceral leishmaniasis mortality is high at the community and the Tribal ethnic population is at highest risk for visceral leishmaniasis death. The national visceral leishmaniasis elimination program should give special attention to the tribal community in the visceral leishmaniasis endemic areas in Bangladesh and the existing surveillance systems needs to be improved by integrating active case detection and active follow-up of the treated patient's.

**Key words:** Visceral leishmaniasis, Mortality, Verbal Autopsy, Tribal, Bangladesh

**Strength and limitation of the study**

**Strength**

- This is the first study in the South East Asia Region, in which we investigated the VL related mortality in Bangladesh using verbal autopsy procedure.

**Limitation**

- The study is limited to only two unions of endemic districts.
- The recall bias in the study cannot be excluded, but we tried to minimize it as much as possible by probing with different events occurred during last 2 years from the date of interview

## Introduction

Leishmaniasis one of the most important vector-borne diseases with an estimated 1.98 million disability adjusted life years and 20000 to 40000 deaths per annum<sup>1,2</sup>. Recent empirical estimate show that worldwide about 0.2 to 0.4 and 0.7 to 1.2 million Visceral leishmaniasis (VL) and Cutaneous leishmaniasis (CL) cases occurred respectively each year<sup>1</sup>. Ninety percent of the global burden of VL is found in six countries, India, Bangladesh, Sudan, South Sudan, Brazil and Ethiopia<sup>1</sup>. There are an estimated 200 million population at risk in the Indian subcontinent, which reports 25 000 to 40 000 cases and 200-300 deaths every year<sup>3</sup>. For many years, there has been a substantial number of VL cases that have never been reported due to lack of proper surveillance systems which make the disease neglected. In Bangladesh, VL re-emerged in early eighties and since then there has been more than 90000 VL cases documented<sup>4,5</sup>. The reported VL incidence in Bangladesh ranges from 7000–9000 cases per year since 1996 and is likely s significant underestimated<sup>6</sup>. After adjusting the substantial under reporting factor, the recent estimated VL incidence in Bangladesh ranges from 12400–24900 cases per year<sup>1</sup>. The disease affects about 45 districts in Bangladesh, however most of the cases are reported from the Mymensingh District<sup>4,5</sup>. The female *Phlebotomas argentipes* sand fly is the only vector; humans are the only reservoir and *Leishmania donovani* is the only species responsible for VL in the Indian subcontinent, including Bangladesh<sup>3-5</sup>. The disease is fatal if not treated. Even with treatment the mortality rate is high (10%)<sup>7</sup>. In 2005, a national VL elimination program has been launched jointly by the Health Ministries from Bangladesh, India and Nepal to eliminate VL by 2015<sup>8</sup>. The goal of the elimination program is to reduce VL cases below 1 per 10,000 people in the VL endemic areas<sup>8</sup> through active case detection, proper management of cases of VL and Post-kala-azar Dermal Leishmaniasis (PKDL) and interruption of disease transmission through integrated vector management strategies, and social mobilization<sup>8,9</sup>. To support the national elimination program in Bangladesh, several operational research programs have been conducted since 2006 by government and non-government partner organizations. These research findings revealed that the passive case detection (existing surveillance system) highly under estimated cases compared to

active case detection in Bangladesh<sup>10-12</sup>. The study conducted in the Rajshahi District also showed that the incidence of VL was 27 higher than the elimination target in 2008 and the knowledge of the disease, its vectors and health seeking behavior was poor<sup>12</sup>.

Similar to VL case reporting, it can be assumed that the mortality rate of VL is also highly underestimated in Bangladesh. Until now, there is no well designed study to measure actual VL mortality in Bangladesh. According to the Directorate General of Health Services, the reported annual number of VL deaths varied from 6 to 36 during 1999-2009<sup>13</sup>, which seems to be highly under estimated as compare to a small area community based study which reports high mortality (about 10.0%) in 2003<sup>14</sup>. The possible reason for highly underestimation of VL death reporting in Bangladesh might be because of shortfall in passive the reporting system. It is most likely that VL patients who are poor and living in remote communities far from heath care facilities often die at home without seeking treatment. Another important cause of underestimation of VL deaths is that patients from tribal community don't seek medical care at the hospital due to cultural beliefs and prefer to stay home or go to the traditional healers and die at home. These points are not considering in the existing surveillance system in Bangladesh which makes VL a neglected disease due to its low mortality rate as reported by existing passive surveillance. Thus, there is a need to investigate the mortality rate by VL through active surveillance. Culturally, autopsy is not well accepted in Bangladesh. However verbal autopsy (VA) could be the alternative since it is the best available approach for assessing causes of death in communities where most deaths occur at home [7].

There has been no study conducted to date to investigate the actual VL mortality in the Indian subcontinent including Bangladesh. We have therefore undertaken this study to fill this knowledge gap in Bangladesh. The objective of our study is to estimate the actual VL mortality and risk factors in two geographically and culturally different VL endemic regions in Bangladesh.

## Methods

### Study sites and population

The study was carried out in two different VL endemic Upazilas (sub-districts); Trishal and Godagari from **July 2011 to December 2011**. The Trishal Upazila is located at 24.5792742°N 90.3950388°E under the Mymensingh District, which is about 120 km north of the capital city, Dhaka of Bangladesh. The Upazila consists of 12 union parishads and 160 villages. Another study Upazila, Godagari is located at 24.4667°N 88.3306°E under the Rajshahi District in the north-western part of Bangladesh. This Upazila consists of nine union parishads and 396 villages with different ethnic populations. Two Unions from these Upazilas were included in the study where all the households were enrolled after obtaining written consent from the head of household.

### Sample size estimation

It was reported that the VL case fatality rate was about 10% in 2003 in VL endemic areas in Mymensingh District<sup>14</sup>. We assumed significant reduction of case fatality rate alone with the reduction of VL incidence as a benefit of VL elimination program in Bangladesh which has been launched in 2006. The sample size has been calculated assuming 6.5% VL case fatality rate in the endemic areas in Bangladesh. To demonstrate the VL case fatality rate of 6.5 % with +/-3.0% precision and 95% confidence interval, a total of 191 VL case was needed from the study areas. Assuming an annual VL incidence of about 10 per thousand population in the endemic areas, a minimum of 19,100 population was required for the study. We studied a population of 24934 from Trishal Upazila and 26160 from Godagari Upazila (a total of 51094 population) which gave sufficient power to the study.

### Study design and sampling

The study design was retrospective cross sectional. Two study arms were identified firstly, one was Godagari Upazila from the Rajshahi District with a tribal-ethnic community and another was the Trishal Upazila from the Mymensingh District without any Tribal-ethnic community. There were five VL endemic Unions out of nine Unions in Godagari whereas all 12 Unions in Trishal were endemic for VL. For each Upazila, one endemic Union was selected randomly from all the endemic Unions in the corresponding Upazilas for the study (Figure 1). Before starting the survey, Field Research Assistants (FRAs) were trained on data collection procedures. The trained FRAs visited each household in the study area and collected socio-demographic information from all family members after obtaining written consent form household head. During their visit, they also identified household with past history of VL, any death as well as suspected VL death within the last two years. We defined a suspected VL death as a death with a history of VL treatment or a death with an illness associated with two or more weeks of fever, plus at least one of the following: weight loss, abdominal fullness, abdominal pain, and/or skin darkening. Then the VA method was applied to confirm the suspected VL death. The household with experience of VL death confirmed by VA was defied as VL death households. Households with a past history of VL but no deaths in last two years was defined as a VL cured household (Figure-1). Household head for both the VL death and VL cured households were interviewed by the FRAs with a structured questionnaire to determine their socio-economic status; knowledge concerning VL and about treatment seeking behavior. At the same time, the coordinates (longitude and latitude) of all the households in the study area were recorded using eTrex Venture Garmin single handheld GPS receivers.

**Verbal Autopsy at suspected VL death household**

The FRAs identified the suspected household with a VL death within the last 2 years since the suggested timing for VA is within 3 months to 2 years<sup>15</sup>. After identifying the household with a suspected VL death, a VL expert physician visited immediately along with a FRA to confirm whether the death was due to VL by using the VA method. We developed the interview questionnaire for VA followed by an ICD 10



verbal autopsy guideline and the questionnaire was reviewed by VL expert. We also translated the questionnaire into local languages for the interviews which has been further approved by the IRB, icddr, Bangladesh. In short, the tool assessed the identity of the deceased and established the sequences of the events leading to death including signs and symptoms of the illness before death. Respondents for the interview were household head/ close relatives, since experience shows that close relatives rarely refuse to give information, with some survey reporting 100% response rates<sup>16-18</sup>. Before going to interview, the aim of the study was clearly explained and informed consent was obtained from the respondent. Another specialized physician with local experience independently reviewed each VA questionnaire and indicated whether the cause of death was VL or not. In case of disagreement, the questionnaires were reviewed by a third expert physician, and his verdict was final.

### Statistical analysis

All data was entered and stored in a well checked data entry program developed by EPI Info software (Centers for Disease Control and Prevention, Atlanta, GA). Data was cleaned and checked for duplicates. Descriptive statistics are explored to consider the nature of data. Comparison of outcome variable distribution between VL death and VL cured household has done using parametric and non-parametric approaches, where applicable. Socio-economic, knowledge about VL and health seeking behavior of household head related variables were dichotomized before including in bivariate analysis. Variable significant ( $P \leq 0.05$ ) associated with outcome VL death household in the bivariate analysis (Pearson's chi square and Fisher exact tests, where applicable) were included in a logistic regression procedure. The final model was obtained by a backward selection strategy recommended by Kleinbaum et al.<sup>19</sup>. The analysis was carried out using the statistical software SPSS 13.0 for windows (SPSS, Chicago, IL, USA). The study area map with spatial distribution of households in the study areas was created by using ArcView GIS version 3.2 (ArcGIS, ESRI, USA).

**Results**

**Socio-demographic characteristics of the study population**

A total of 51094 population (12032 households) was studied where 26160 population (6566 households) came from the Rishikul Union under, Godagari, Rajshahi. Average age of the study population was 25.6 years (SD, 18.4) and 49.7% were female (Table-1). About 16 % (n=4243) of the population was tribal in Godagari whereas all the people are non-tribal (Bangali ethnicity) in the Trishal area (Table-1).

**VL-associated mortality based on verbal autopsy**

It was found that 0.4% (n=196) VL occurred out of the total population in the study areas during August 2009 – December, 2011, where 0.5 % (n=137) were found in the Trishal Upazila and 0.2 % (n=59) in the Godagari Upazila. Twenty-five suspected VL death was identified in the household survey by FRAs. Among them, 10 and 2 VL deaths (in total 12) were confirmed by VA which corresponds 17.0% (12/59) and 1.5% (2/137) case fatality rate (CFR) for Godagaria Upazila and Trishal Upazila respectively (Table-2). Significant, a VL CFR difference was observed between the Godagari and Trishal Upazila (16.95 Vs 1.46, P<0.0001). VL CFR in Tribal (22.2%) population is about 17 times higher than the non-tribal/Bangali ethnic (1.3%) population (P<0.0001). It was also found that VL proportionate death accounted for 3.0% (12/382) of the total deaths in the study areas. About six percent of CRF was found as an overall estimate of Godagari and Trishal study areas. Group specific as well as overall CFR are presented in the Table-2.

Among 12 confirmed VL deaths, 50% (n=6) were children aged below 17 years and 75% were male (n=9). Most of the deaths occurred in tribal ethnic populations which accounted for 88.3% (10/12) of total death. About thirty-three percent (4/12) of all confirmed deaths didn't receive any treatment during the

illness that led to death. Tuberculosis as an associated illness was found in eight percent (1/12) of the deceased. The majority of the deaths occurred at home (Table-3). Spatial distribution of households with VL and VL death during August 2009 – December, 2011 are shown in the figure 2.

### Factor associated with the VL death

To identify factors associated with VL death household we compare household related information between 11 VL death households and 154 VL cured households. Bivariate association showed that households with a VL death significantly differ between Tribal-ethnic and Bengali ethnic groups ( $P<0.0001$ ). The VL death households were socio economically poorer than VL cured households as significant difference observed on household head occupation, income and housing structure (Table-4). The level of knowledge was about VL was almost the same between the two groups as no significant association found in bivariate analysis. Although general health seeking behavior of VL death and VL cured household was the same ( $P=0.431$ ), however VL health seeking behavior differ significantly between these two groups ( $P=0.013$ ) (Table-4). About 96% of VL cured households visited qualified doctors when anyone in the family had VL whereas only 63.4% ( $n=7$ ) of VL death households visited qualified doctor for the same.

Through the use of the logistic regression model, only ethnicity was identified as an independent risk factor associated with VL death households. Adjusted model showed that household of Tribal-ethnicity was at 18 (OR=18.1, 95% CI, 3.6-90.6) times higher risk of having a VL death than household with Bengali-ethnicity ( $P<0.0001$ ) (Table-5).

### Discussion

Our study is the first study to estimate the actual mortality of VL in Bangladesh through the VA, and the major findings for the study is that VL mortality in the endemic community is higher than previously thought. Our study also suggests that the tribal population are at high risk of VL death since VL mortality of the tribal population in Rajshahi is very high compared to the most endemic district of Mymensingh, which contributes about 60% of the national VL disease burden <sup>5</sup>. The findings of our study is very important for the national VL elimination program in terms of making more effective program planning to achieve the elimination goal in Bangladesh.

**Comparison with other studies**

It is alarming that the case fatality rate is very high in the Tribal community in Rajshahi which was found to be about 22% (10/45). The probable cause of the high VL CFR in that community could be their poor health seeking behaviors as they rarely visit government hospitals due to cultural believes and prefer traditional healers <sup>20</sup>. As a result, VL patients in that community remain untreated and die at home. We found that 4 out of 12 confirmed VL deaths (about 33%) were not treated before dying and all the untreated belonged to the Tribal community in Rajshahi. A previous study <sup>12</sup> conducted at the same community also identified a lack of access to proper health care, including high delay in VL diagnosis and treatment. Although Mymensingh is highly endemic for VL, the CFR of VL patients living in Mymensingh (all are Bangali ethnic) was not as high as the CFR in Rajshahi district. Additionally, we found low VL mortality in Mymensingh as compared to the reported VL mortality in 2003 <sup>14</sup>. The present VL mortality in Mymensingh could be due to the attention of this highest endemic area by the national VL elimination program in Bangladesh.

The hospital based VL CFR is substantially under estimated in the Indian subcontinent, including Bangladesh <sup>1</sup>. In Bangladesh, the existing hospital based surveillance system is mainly based on the passive reporting system. There is no active follow-up of the VL patients who completed the treatment at the hospital. As a result, the patients who died at the community/home are missed by the existing

surveillance systems. Our study revealed that 4 (50%) died at home out of 8 VL deaths who received treatment at the hospital before death. The other four died at home without treatment at the hospital. Therefore it is important to improve the existing surveillance system by integrating active case detection as well as the active follow-up for the VL patients who are admitted to the hospital for treatment. Another important finding of the study is that about eight percent (1/12) of VL deceased had tuberculosis which indicates the existence of VL-Tuberculosis co-infection in VL endemic areas in Bangladesh. The evidence of VL associated with tuberculosis has been reported in several VL endemic countries, including India<sup>21</sup>. However this type of data has not been previously reported from Bangladesh.

Although there are previous reports<sup>22-24</sup> about clinical risk factors for VL death, so far our study is the first where household level risk factors were explored. The households with VL deaths were found to be socio economically poorer than households without VL deaths. Also poor VL health seeking behavior was observed in the household with VL deaths. Tribal household was the only independent dominating risk factor of having a VL death as determined by the adjusted regression model. This is because the tribal ethnic populations are comparatively poorer, less educated and less aware about health care compare to the Bengali ethnic population.

### Strength and limitation of the study

This is the first study in the South East Asia Region, in which we investigated the VL related mortality in Bangladesh using verbal autopsy procedure. However, the study is limited to only two unions of endemic districts. The recall bias in the study cannot be excluded, but we tried to minimize it as much as possible by probing with different events occurred during last 2 years from the date of interview.

### Conclusion

Our study highlights that VL mortality is high in the community and tribal ethnic populations are at higher risk for VL death. A substantial number of VL patients never visit hospital for proper health care and die at home. The national VL elimination program should give special attention to the tribal community in the VL endemic areas of Bangladesh and the existing surveillance systems needs to be improved by integrating active case detection as well as the active follow-up of the treated patient's.

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**Contributions**

MMH, and DM Conceived and design the study. MMH, RC, APD, SKB and DM wrote the paper; MMH performed the statistical analysis, DG participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript. MMH is the study guarantor.

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## Competing interests

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

## Ethical Approval

The study was approved by the institutional Ethical Review Committee of icddr,b, Dhaka, Bangladesh (Research Protocol # PR-11027). All households in the study areas were enrolled in the study after obtaining written consent from the head of the household. Informed consent was obtained from the respondent (head of household/close relatives) before conducting verbal autopsy.

## Transparency

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained

## Data Sharing

No additional data available.

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**What is already known to this topic**

The case fatality rate was 1.5% and about 10.0% respectively by hospital base surveillance from 2004 to 2008 and from a community based study conducted in 2002-2004. In the study the case fatality rate of VL was related with gender.

**What is study adds**

The VL case fatality rate was unknown after introduction of VL elimination program. Current study showed that the overall case fatality rate was 6.2% which is still high. The tribal populations are highly vulnerable to VL death (CRF, 22.2%). Tuberculosis as co-infection also contributed to VL related death.



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Tables

Table-1: Socio-demographic characteristics and history of VL and death in the study population

	Trishal, Mymensingh	Godagari, Rajshahi	Total
Total Population	24934	26160	51094
Total household	5466	6566	12032
Mean Age (SD)	24.53 (18.91)	26.70 (17.92)	25.65 (18.44)
Age ratio			
<17 years	10868 (43.6)	9309 (35.6)	20177 (39.5)
17-45 years	10091 (40.5)	12895 (49.3)	22986 (45.0)
>45 years	3975 (15.9)	3956 (15.1)	7931 (15.5)
Male population	12958 (52.0)	13267 (50.7)	26225 (51.3)
Ethnicity			
Bangali	24934 (100.0)	21917 (83.8)	46851 (91.7)
Tribal	00 (0.0)	4243 (16.2)	4243 (8.3)
Past h/o VL in last 2 years	137 (0.5)	59 (0.2)	196 (0.4)
Total death reported by respondent in last 2 years	208	174	382
Total suspected VL death in last 2 years	3	22	25
Total VL death in last 2 years confirmed by VA	2	10	12

Table-2: Visceral leishmaniasis cases and mortality in Bangladesh, August 2009 – December, 2011

	Trishal, Mymensingh				Godagari, Rajshahi				Overall			
	Population	VL case	VL death	Mortality	Population	VL case	VL death	Mortality	Population	VL case	VL death	Mortality
<b>By sex</b>												
Female	11976	50	1	2.0%	12893	22	2	9.09%	24869	72	3	4.17%
Male	12958	87	1	1.15%	13267	37	8	21.62%	26225	124	9	7.26%
<b>By age</b>												
Child	11091	74	0	0.0%	9687	30	6	20.0%	20778	104	6	5.77%
Adult	13843	63	2	3.17%	16473	29	4	13.79%	30316	92	6	6.52%
<b>By ethnicity</b>												
Tribal	0	0	0	0.0%	4243	45	10	22.22%	4243	45	10	22.22%
Bangali	24934	137	2	1.46%	21917	14	0	0.0%	46851	151	2	1.32%
<b>Overall</b>	24934	137	2	1.46%	26160	59	10	16.95%	51094	196	12	6.12%

Table-3: Characteristics of VL deceased confirmed by verbal autopsy

	VL deceased; n (%)		
	Male N=9	Female N=3	Overall N=12
Age group			
<17 years	4 (44.4)	2 (66.7)	6 (50.0)
17-45 years	5 (55.6)	1 (33.3)	6 (50.0)
>45 years	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity			
Tribal	8 (88.9)	2 (66.7)	10 (88.3)
Bangali	1 (11.1)	1 (33.3)	2 (16.7)
Received treatment before death	5 (55.6)	3(100.0)	8 (66.7)
Having TB co-infection	0 (0.0)	1 (33.3)	1 (8.3)
Place of death			
Home	7(77.8)	2(66.7)	9 (75.0)
Hospital	2(22.2)	1(33.3)	3 (25.0)

**Table-4: VL death and VL cured households and the bivariate analysis for socio-economic, VL knowledge and health seeking behavior related information**

	VL Death HH N=11 n (%)	VL Cured HH N=154 n (%)	P-Value
Study site			
Mymensingh	2 (18.2)	115 (74.7)	<b>&lt;0.0001</b>
Rajshahi	9 (81.8)	39 (25.3)	
Socio economic status			
Illiterate HH head	6 (54.5)	74 (48.1)	0.677
Labor HH head	10 (90.9)	64 (41.6)	<b>0.003</b>
Income about <100 USD	11 (100.0)	101 (65.6)	<b>0.017</b>
Precarious house	10 (90.9)	83 (53.9)	<b>0.024</b>
Living room with <2	7 (63.6)	67 (43.5)	0.223
Family size with <5 members	2 (18.2)	57 (37.0)	0.331
Having bed-nets	11 (100.0)	98.7 (152)	1.00
Having domestic animals	10 (90.9)	130 (84.4)	1.00
Knowledge about VL			
Symptoms	11 (100.0)	136 (88.3)	0.611
Transmitted by mosquito/sand fly	6 (54.5)	71 (46.1)	0.588
The disease is curable	11 (100.0)	147 (95.5)	1.000
Health seeking behaviors			
Visit qualified provider when get any sick	1 (9.1)	7 (4.5)	0.431
Visit qualified provider when get VL	7 (63.4)	142 (92.2)	<b>0.013</b>
Ethnicity			
Bengali	2 (18.2)	127 (82.5)	<b>&lt;0.0001</b>
Tribal	9 (81.8)	27 (17.5)	

*HH refers household*

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Table-5: Independent risk factor on visceral leishmaniasis death (OR adjust using stepwise logistic regression)

Variable	VL death HH	VL cured HH	Odds ratio	(95% CI)	Adjusted odds ratio <sup>s</sup>	(95% CI)	P- value
Ethnicity							
Tribal	9	27	21.2	(4.3 –103.5)	18.1	(3.6–90.6)	<0.0001
Bangali	2	127	1.00		1.00		
VL health seeking behavior							
Unqualified doctor	4	12	6.8	(1.7–26.4)	4.3	(1.00–20.5)	0.063
Qualified doctor	7	142	1.00		1.00		

HH refers household  
\$ adjusted by study location, household head occupation, income, housing structure



## Figures

*Figure-1: Study profile*

*Figure-2: study area map including spatial distribution of households, households with VL and VL death during August 2009 – December, 2011*

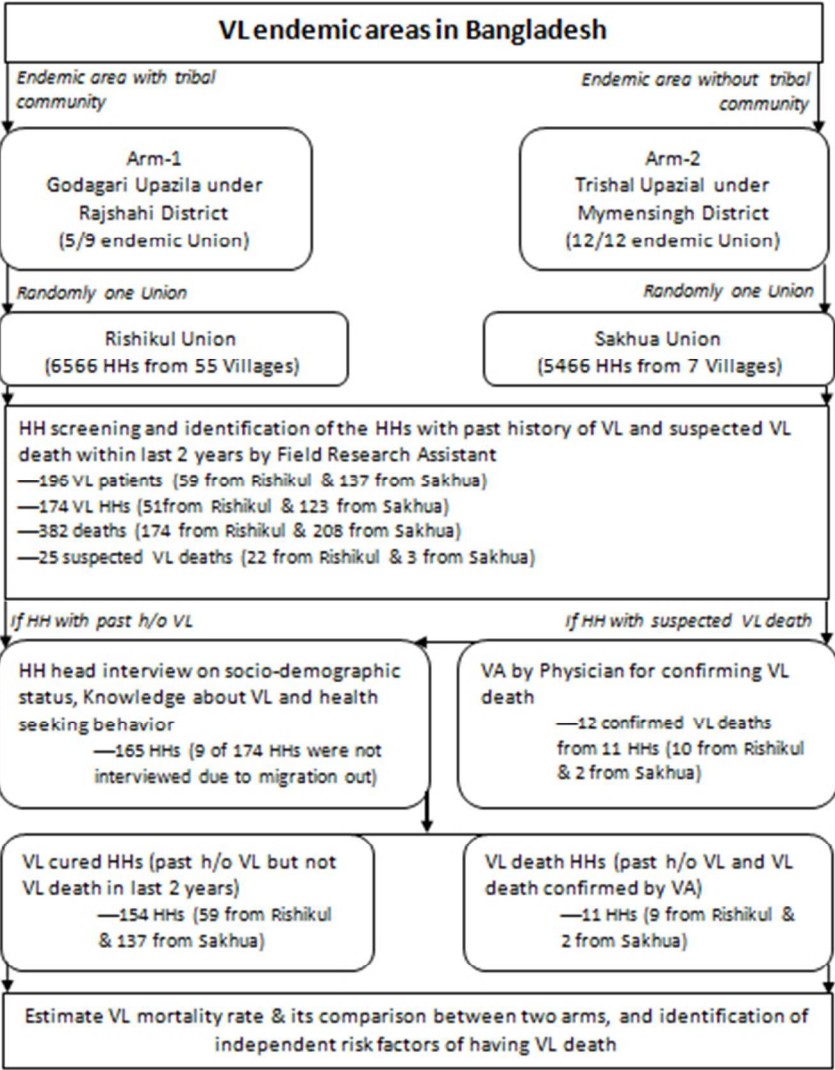


Figure-1: Study profile

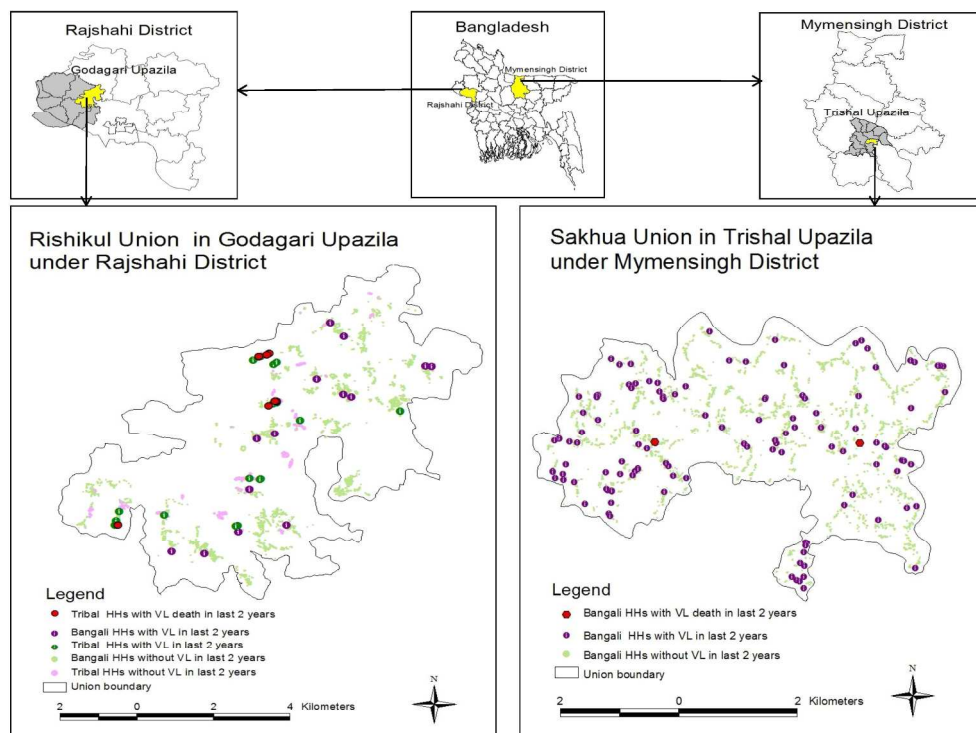


Figure-2: study area map including spatial distribution of households, households with VL and VL death during August 2009 – December, 2011  
714x535mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Checklist
<b>Title and abstract</b>	1	(a) Done, see “Title” (b) Done, see “Abstract”
<b>Introduction</b>		
Background/rationale	2	Done, see “Introduction”
Objectives	3	Done, see “Introduction”
<b>Methods</b>		
Study design	4	Retrospective cross-sectional study. See “Study design and sampling” and Figure 1
Setting	5	Done, see “ Study site and population”
Participants	6	(a) Retrospective cross-sectional study — mention in “Study design and sampling” See figure 1
Variables	7	VL death confirmed by verbal autopsy procedure; History of VL in last two years; Socio demographic, Socio-economic and knowledge concerning VL and about treatment seeking behavior.
Data sources/ measurement	8*	Data were collected by research team from the study areas. See “Method”
Bias	9	Random selection of the study area. See “Figure 1”
Study size	10	Done, see “Sample size estimation”
Quantitative variables	11	Done, see “Statistical analysis”
Statistical methods	12	(a) Done, see “Statistical analysis” (b) Done, see “Statistical analysis” (c) Explain how missing data were addressed, Not applicable <i>Cross-sectional study</i> — Done, see “Statistical analysis” (e) Not applicable
<b>Results</b>		
Participants	13*	(a) Done, see “Results” and “Figure -1” (b) See “Figure-1” (c) See “Figure-1”
Descriptive data	14*	(a) Done, See “Results” and “Table-1”, “Table-2” & “Table-3” (b) Not applicable (c) <i>Not applicable</i>
Outcome data	15*	<i>Not applicable</i> <i>Case-control study</i> —Done see “Results” and “Table-4” <i>Cross-sectional study</i> —Done, see “Results” and “Table-2”
Main results	16	(a) Done, see “Results” and “Table-2” & “Table-5” Not Applicable Not Applicable
Other analyses	17	Not Applicable
<b>Discussion</b>		
Key results	18	Done, see “Discussion”
Limitations	19	Done, see “Discussion”

Interpretation	20	Done, see “Conclusion”
Generalisability	21	Done, see “Comparison in Discussion”
<b>Other information</b>		
Funding	22	Done, see Funding

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

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# Visceral leishmaniasis associated mortality in Bangladesh: A retrospective cross-sectional study

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## Abstract

**Objective:** To investigate visceral leishmaniasis (VL) death and risk factors in two VL endemic areas of Bangladesh

**Design:** Retrospective cross sectional

**Setting:** Two geographically and culturally different VL endemic sub-districts, Godagarai in the District of Rajshahi and Trishal in the District of Mymensingh in Bangladesh, August 2009 – December, 2011

**Participants:** 51094 inhabitants from randomly selected Unions in the two sub-districts.

**Main outcome measures:** VL deaths, confirmed independently by qualified physicians using the Verbal Autopsy procedure ICD10 guideline.

**Results:** The total number of people screened for VL death was 51094 from 12032 households from Godagari and Trishal sub-districts. About 16% of the people from Godagari, were Tribal. The average age of the study population was 25.6 years (SD, 18.4) and 49.7% were female. VL case fatality rate averaged 6.12% (12/196) including 2/137 in Trishal and 10/59 in Godagari. Most of the VL deaths (9/12, 75%) occurred at home and the rest in tertiary hospitals. None of these deaths had been reported in the national VL surveillance system. VL case fatality rate in the Tribal ethnic (22.2%) population was about 17 times higher than the Bangali ethnic (1.3%) population ( $P<0.0001$ ). Tribal-ethnicity had 18 times ( $OR=18.1$ , 95% CI, 3.6-90.6) higher risk for VL death compared to Bangali ethnicity ( $P<0.0001$ ).

**Conclusion:** VL deaths were found to be high in the study areas and was underreported. The Tribal ethnic population was at highest risk for VL death. The national VL elimination program should give special attention to the tribal community in the endemic areas especially for those in Godagari, Rajshahi and should strengthen VL surveillance by including tertiary hospitals in the national surveillance system.

**Key words:** Visceral leishmaniasis, Mortality, Verbal Autopsy, Tribal, Bangladesh



**Strength and limitation of the study**

**Strength**

- This is the first study in the South East Asia Region, in which VL related mortality was investigated in Bangladesh using the verbal autopsy procedure.

**Limitation**

- The study is limited to only two unions of endemic districts.
- The recall bias in the study cannot be excluded, but we tried to minimize this by probing with different events occurred during last 2 years from the date of interview.

## Introduction

Leishmaniasis one of the most important vector-borne diseases with an estimated 1.98 million disability adjusted life years and 20000 to 40000 deaths per annum<sup>1,2</sup>. Recent empirical estimates found the annual incidence of Visceral Leishmaniasis (VL) and Cutaneous Leishmaniasis (CL) to be 0.2 - 0.4 and 0.7 -1.2 million cases respectively<sup>1</sup>. Ninety percent of the global burden of VL occurred in India, Bangladesh, Sudan, South Sudan, Brazil and Ethiopia<sup>1</sup>. The estimated population at risk for VL is 200 million with and annual incidence of 25-40000 and number of death about 2-300<sup>3</sup>. For many years, there has been a substantial number of VL cases that have never been reported due to lack of proper surveillance systems which contributes to the neglect of this disease.

In Bangladesh, VL re-emerged in the early eighties and since then more than 90000 cases have been documented<sup>4,5</sup>. Since 1996 the reported VL incidence in Bangladesh has ranged from 7 – 9000 cases per year, but this is likely to be underestimated<sup>6</sup>. After adjusting the substantial under reporting factor, the recent estimated VL incidence in Bangladesh ranges from 12,400–24,900 cases per year<sup>1</sup>. The disease is prevalent in 45 districts of Bangladesh, however most of the cases are reported from the Mymensingh District<sup>4,5</sup>. The female *Phlebotomus argentipes* sand fly is the only vector; humans are the only reservoir and *Leishmania donovani* is the only species responsible for VL in the Indian subcontinent, including Bangladesh<sup>3-5</sup>. The disease is fatal if not treated. Even with treatment the mortality rate is high (10%)<sup>7</sup>. In 2005, a national VL elimination program has been launched jointly by the Health Ministries from Bangladesh, India and Nepal to eliminate VL by 2015<sup>8</sup>. In Bangladesh the goal of the elimination program is to reduce VL cases below 1 per 10,000 people in the VL endemic sub-districts (known as Upazila)<sup>8</sup>. The strategies for VL elimination includes active detection of VL and Post-kala-azar Dermal Leishmaniasis (PKDL) cases, adequate treatment of VL and PKDL cases, interruption of disease transmission through integrated vector management, and social mobilization<sup>8,9</sup>. Since 2006, several operational research activities have been conducted by government and non-government organizations to

support the national elimination program in Bangladesh. These programs revealed that the passive case detection (existing surveillance system) highly under estimated VL cases in Bangladesh <sup>10-12</sup>. In 2008 a study conducted in the Rajshahi District showed that the incidence of VL was 27 times higher than the elimination target. It also found that the knowledge of the community people about VL and its vector was poor and their health seeking behavior was also unsatisfactory <sup>12</sup>.

Similar to VL case reporting, it can be assumed that the mortality rate of VL is also highly underestimated in Bangladesh. Until now, there is no well designed study to measure VL mortality in highly VL endemic areas of Bangladesh. According to the Directorate General of Health Services, the reported annual number of VL deaths varied from 6 to 36 during 1999-2009 <sup>13</sup>. This appears to be highly under estimated because a community based study in a small endemic area reported a high VL mortality rate (about 10.0%) in 2003 <sup>14</sup>. The possible reason for the high underestimations of VL death might be a shortfall in the passive reporting system which does not include tertiary hospitals under VL case surveillance. VL patients who are poor and living in remote communities far from health care facilities often die at home without seeking treatment or preferred traditional healer for their health care and do not report to the public health facilities. Underestimation of deaths contributes to VL remaining a major neglected tropical disease. Thus, there is a need to investigate the magnitude of VL deaths and its risk factors through a well designed study and using adequate tools for investigation of death. Culturally, autopsy is not well accepted in Bangladesh. Verbal autopsy (VA) could be the alternative since it is the best available approach for assessing causes of death in the communities where most deaths occur at home<sup>7</sup>. Until now no study has been conducted to investigate the VL deaths in the Indian subcontinent including Bangladesh after the start of the VL Elimination Program. We have therefore undertaken this study to fill this knowledge gap in Bangladesh. The objective of this study is to estimate the VL mortality and risk factors in two geographically and culturally different highly VL endemic areas of Bangladesh.

## Methods

### Study sites and population

The study was carried out in the two different VL endemic areas of Bangladesh; Godagari sub-district in the district of the Rajshahi and the Trishal sub-district in the Mymensingh district. Both Trishal and Godagari are highly endemic for VL. The study activities was performed from July 2011 to December 2011. Mymensingh district reports more than 60% of total VL cases in the country. The Trishal is one of the five most VL endemic sub-districts in Mymensingh and is located at 24.5792742°N 90.3950388°E . Trishal consists of 12 unions and 160 villages and all the unions are endemic for VL. Godagari is one of the highest VL endemic sub-districts in Rajshahi which is located at 24.4667°N 88.3306°E with 9 unions and 396 villages and has a significant tribal population. Godagari was included in the study was to investigate the VL death among tribal populations and to compare it with that of the Bangali ethnic population. Based on our past experiences, we assumed that the tribal population was at higher risk for VL deaths.

### Sample size estimation

It was reported that the VL case fatality rate was about 10% in 2003 in VL endemic areas in Mymensingh District<sup>14</sup>. We assumed a significant reduction of case fatality rate along with the reduction of VL incidence as a benefit of VL elimination program in Bangladesh. We therefore calculated the sample size assuming an average of 6.5% case fatality rate (CFR) with +/-3.0% precision and 95% confidence interval (CI). A total of 191 VL cases was needed to obtain a 6.5% CFR in the study areas. To obtain a minimum of 191 past VL cases in the last 2 years, the survey required a total of 47750 people

(considering annual VL incidence 20 per 10000). The study areas included a population of 51094 (24934 from Trishal and 26160 from Godagari).

**Study design and sampling**

The study design was retrospective cross sectional. As mentioned above, we selected Trishal and Godgarai sub-districts and one endemic union from each sub-district was taken randomly (Figure1). The trained field research assistants (FRAs) visited each household, made household rosters and collected socio-demographic information from the head of the household. During their visit, FRAs also identified households with past cases of VL, any death and suspected VL death within the last two years. To minimize recall bias, the FRAs used probing with different events (mainly religious festivals) occurred during last 2 years from the date of interview. We defined a suspected VL death as a death with a history of VL treatment or a death with an illness associated with two or more weeks of fever, plus at least one of the following: weight loss, enlarged abdomen, abdominal pain, and/or skin darkening. Then the VA method was applied to confirm the suspected VL death (please see below). The household with VL death confirmed by VA was defined as VL death households. Households with a past history of VL but no deaths in last two years was defined as a VL cured household (Figure-1). Household heads from both VL death and VL cured households were interviewed by the FRAs with a structured questionnaire for collection of information about the household's socio-economic status, knowledge about VL and its vector, and for information about the treatment seeking behavior used. At the same time, the coordinates (longitude and latitude) of all the households in the study area were recorded using eTrex Venture Garmin single handheld GPS receivers.

## Verbal Autopsy at suspected VL death household

We developed the interview questionnaire for VA followed by an ICD 10 verbal autopsy guideline and the questionnaire was reviewed by a VL expert. We also translated the questionnaire into local language which has been further reviewed, revised and approved by the icddr,b Ethical Review Committee. Briefly, the tool assessed the identity of the deceased and established the sequences of the events leading to death including signs and symptoms of the illness before death. It is recommended that VA should be done within 3 months to 2 years to minimize recall bias<sup>15</sup>. After identifying the household with a suspected VL death, a VL expert physician visited the household immediately with a FRA and conducted the VA. Respondents for the interview were household head/ close relatives. Studies with VA showed that close relatives rarely refuse to give information and some situations response rates were 100%<sup>16-18</sup>. A second VL expert physician reviewed each VA questionnaire independently. In case of disagreement between first and second physician, the VA questionnaires were reviewed by a third expert physician and his verdict was final.

## Statistical analysis

All data was entered and stored in a well checked data entry program developed by EPI Info software (Centers for Disease Control and Prevention, Atlanta, GA). Data was cleaned and checked for duplicates. We explored the descriptive statistics to consider the nature of data. We calculated case fatality rate (CFR) and compared the rates between different study sites (Godagari versus Trishal) and ethnic groups (Tribal versus Bangali) with the Z-test. Socio-economic, knowledge about VL and health seeking behavior of each household head related variables were dichotomized before including in bivariate analysis. Variable significantly ( $P \leq 0.05$ ) associated with outcome VL death household in the bivariate analysis (Pearson's chi square and Fisher exact tests, where applicable) were included in a logistic regression model. The final model was obtained by a backward selection strategy recommended by Kleinbaum et al.<sup>19</sup>. The statistical software, SPSS 13.0 for windows (SPSS, Chicago, IL, USA) was used

to carry out all the analysis. We constructed the study area map with spatial distribution of households in the study areas by using ArcView GIS version 3.2 (ArcGIS, ESRI, USA).

## Results

### Socio-demographic characteristics of the study population

A total of 51094 people (12032 households) were studied where 26160 (6566 households) came from the Rishikul Union in the subdistrict of Godagari in the district of Rajshahi and rest of the people from Sakhua Union in the sub-district of Trishal in the Mymensingh district. The average age of the study population was 25.6 years (SD, 18.4) and 49.7% were female (Table 1). About 16 % (n=4243) of the population was tribal in Godagari whereas all the people are non-tribal (Bangali ethnicity) in the Trishal area (Table-1).

### VL-associated mortality based on verbal autopsy

During the period August 2009 – December, 2011, VL affected 0.4% (196/51094) of the people in the study areas. The proportion of the VL affected population was higher in Trishal (0.5 %, 137/24934) compare to Godagari (0.2%, 59/26160). Trained FRAs suspected a total of 25 VL deaths and VL expert physicians confirmed VL deaths in 12/25 by VA. The VL deaths in two areas averaged 6.12% (12/196) and accounted for 3.14% (12/382) of the total deaths in the study areas. The VL CFR differed significantly from Godagari than Trishal and was 17.0% (12/59) and 1.5% (2/137) respectively ( $P<0.0001$ ) (Table-2). The VL CFR in the Tribal population (22.2%) was about 17 times higher than the non-tribal/Bangali ethnic (1.3%) population ( $P<0.0001$ ).

Among 12 confirmed VL deaths, 50% (6/12) were children aged below 17 years and 75% (9/12) were male. Most of the deaths occurred in tribal ethnic populations which accounted for 88.3% (10/12) of total

VL deaths. About 33% (4/12) of all confirmed deaths did not receive treatment during their illness that led to death. Tuberculosis as an associated illness was found in eight percent (1/12) of the deceased. The majority of the deaths occurred at home and the rest were in the tertiary hospital (Table-3). When checked for reporting of these 12 VL deaths in the existing VL surveillance system, none were recorded.. The spatial distribution of households with VL and VL death during August 2009 – December, 2011 are shown in the figure 2.

### Factors associated with the VL death

To identify factors associated with VL death households, we compared household related information between 11 VL death households and 154 VL cured households. Bivariate association showed that households with a VL death significantly differ between Tribal-ethnic and Bangali ethnic groups ( $P<0.0001$ ). The VL death households were socio economically poorer than VL cured households demonstrated by significantly more labor occupation of household head, less monthly income and more poor housing structures in VL death households (Table-4). The level of knowledge about VL was however almost the same between the two groups (Table 4). Although general health seeking behavior of VL death and VL cured household was the same ( $P=0.431$ ), their VL health seeking behavior differed significantly ( $P=0.013$ ) (Table-4). About 96% (142/154) of VL cured households visited qualified doctors when members of the family had VL whereas only 63.4% (7/11) of VL death households visited qualified doctors for the same.

The logistic regression model showed that the ethnicity was the only independent risk factor for VL death. The adjusted model showed that households of Tribal-ethnicity were at 18 (OR=18.1, 95% CI, 3.6-90.6) times higher risk of having a VL death than household with Bengali-ethnicity ( $P<0.0001$ ) (Table-5).



**Discussion**

Our study is the first study to estimate the actual mortality of VL in Bangladesh through the VA, and the major findings for the study are : VL mortality in the endemic community remains high, the tribal population are at higher risk for VL death and there is underreporting of VL deaths by the existing VL surveillance system. The findings of our study is very important for the national VL elimination program in terms of making more effective program planning to achieve the elimination goal in Bangladesh.

**Comparison with other studies**

It is alarming that the VL case fatality rate is very high in the Tribal community in Rajshahi which was found to be about 22%. The probable cause of the high VL CFR in that community could be their poor health seeking behaviors as they rarely visit government hospitals due to cultural believes and prefer traditional healers <sup>20</sup>. As a result, VL patients in that community remain untreated and die at home. We found that about 33% confirmed VL deaths were not treated before dying and all the untreated belonged to the Tribal community in Rajshahi. A previous study <sup>12</sup> conducted at the same community also identified a lack of access to proper health care, including high delay in VL diagnosis and treatment. Although Mymensingh is highly endemic for VL, the CFR of VL patients living in Mymensingh (all are Bangali ethnic) was not as high as the CFR in Rajshahi district. Additionally, we found low VL mortality in Mymensingh as compared to the reported VL mortality in 2003 <sup>14</sup>. The less VL mortality in Mymensingh can be explained by more focused attention to this highest endemic area by the national VL elimination program of the country.

The hospital based VL CFR is substantially under estimated in the Indian subcontinent, including Bangladesh <sup>1</sup>. In Bangladesh, the existing hospital based surveillance system is mainly based on the passive reporting system. There is no active follow-up of the VL patients who had been treated in the hospital. As a result, the patients who died in the community/home are missed by the existing surveillance systems. Until recently, the tertiary hospitals did not report VL cases to the national program. Even very

recently only two tertiary hospitals started reporting of VL cases to the national surveillance system. Our study results complied with these facts. Forty two percent (5/12) of VL deaths occurred at home, although they had been treated in the hospitals. Twenty five percent (3/12) died in the tertiary hospitals and the rest 33% (4/12) died at home without treatment. It is surprising that none of these 12 VL deaths were reported by the VL national program even when the deaths occurred in the tertiary hospital. Thus, VL deaths are highly under reported. Therefore there is an urgent need for improvement of the existing surveillance system, implementation of active surveillance of VL patients under treatment and inclusion of the tertiary hospitals (especially those in the VL endemic areas) under a routine VL case reporting mechanism.

Another important finding of the study is that about 8% of VL deceased had tuberculosis which indicates the existence of VL-Tuberculosis co-infection in VL endemic areas in Bangladesh. The evidence of VL associated with tuberculosis has been reported in several VL endemic countries, including India<sup>21</sup>. However this type of data has not been previously reported from Bangladesh.

Although there are previous reports<sup>22-24</sup> on clinical risk factors for VL death, so far our study is the first where household level risk factors were explored. The households with VL deaths were found to be socio economically poorer than households without VL deaths. Moreover, poorer VL health seeking behavior was observed in the households with VL deaths. Tribal households was the only independent dominating risk factor of having a VL death as determined by the adjusted regression model. This is because the tribal ethnic populations are comparatively poorer, less educated and less aware about health care compare to the Bangali ethnic population. The VL elimination program should therefore take necessary actions to improve the VL health seeking behavior of the tribal population especially those in the Rajshahi VL endemic areas to minimize their risk from VL death.

### Strength and limitation of the study

This is the first study in the South East Asia Region which investigated VL related mortality in Bangladesh using the verbal autopsy procedure. The study is however limited to only two unions from the endemic districts. The recall bias in the study cannot be excluded, but we tried to minimize it as much as possible by probing with different events occurred during the last 2 years from the date of interview.

**Conclusion**

This study highlighted VL mortality in two VL endemic areas of Bangladesh, underlined underreporting of VL deaths and found tribal ethnic populations at higher risk for VL death. A substantial number of VL patients never visit hospital for proper health care and die at home. The national VL elimination program should give special attention to the tribal community in the VL endemic areas of Bangladesh and the existing surveillance systems must be improved by integrating active case detection as well as the active follow-up of the treated patient's.

## Acknowledgements

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## Contributions

MMH, and DM Conceived and design the study. MMH, RC, APD, SKB and DM wrote the paper; MMH performed the statistical analysis, DG participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript. MMH is the study guarantor.

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## Competing interests

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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**Ethical Approval**

The study was approved by the institutional Ethical Review Committee of icddr,b, Dhaka, Bangladesh (Research Protocol # PR-11027). All households in the study areas were enrolled in the study after obtaining written consent from the head of the household. Informed consent was obtained from the respondent (head of household/close relatives) before conducting verbal autopsy.

**Transparency**

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained

**Data Sharing**

No additional data available.

## What is already known to this topic

The reported case fatality rate was 1.5% and about 10.0% respectively by WHO estimates based on hospital surveillance from 2004 to 2008 and from a community based study conducted in 2002-2004. In the study the case fatality rate of VL was related with gender.

## What this study adds

The VL case fatality rate was unknown after introduction of the VL elimination program. This study showed that the overall case fatality rate was 6.1% in two VL endemic areas which is considered high. The VL deaths were under reported. The tribal populations are highly vulnerable to VL death (CFR, 22.2%). Tuberculosis as co-infection also contributed to VL related death.

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## Tables

**Table-1: Socio-demographic characteristics and history of VL and death in the study population**

	Trishal, Mymensingh	Godagari, Rajshahi	Total
Total Population	24934	26160	51094
Total household	5466	6566	12032
Mean Age (SD)	24.53 (18.91)	26.70 (17.92)	25.65 (18.44)
Age ratio			
<17 years	10868 (43.6)	9309 (35.6)	20177 (39.5)
17-45 years	10091 (40.5)	12895 (49.3)	22986 (45.0)
>45 years	3975 (15.9)	3956 (15.1)	7931 (15.5)
Male population	12958 (52.0)	13267 (50.7)	26225 (51.3)
Ethnicity			
Bangali	24934 (100.0)	21917 (83.8)	46851 (91.7)
Tribal	00 (0.0)	4243 (16.2)	4243 (8.3)
Past h/o VL in last 2 years	137 (0.5)	59 (0.2)	196 (0.4)
Total death reported by respondent in last 2 years	208	174	382
Total suspected VL death in last 2 years	3	22	25
Total VL death in last 2 years confirmed by VA	2	10	12

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Table-2: Visceral leishmaniasis cases and mortality in Bangladesh, August 2009 – December, 2011

	Trishal, Mymensingh				Godagari, Rajshahi				Overall			
	Population	VL case	VL death	Mortality	Population	VL case	VL death	Mortality	Population	VL case	VL death	Mortality
By sex												
Female	11976	50	1	2.0%	12893	22	2	9.09%	24869	72	3	4.17%
Male	12958	87	1	1.15%	13267	37	8	21.62%	26225	124	9	7.26%
By age												
Child	11091	74	0	0.0%	9687	30	6	20.0%	20778	104	6	5.77%
Adult	13843	63	2	3.17%	16473	29	4	13.79%	30316	92	6	6.52%
By ethnicity												
Tribal	0	0	0	0.0%	4243	45	10	22.22%	4243	45	10	22.22%
Bangali	24934	137	2	1.46%	21917	14	0	0.0%	46851	151	2	1.32%
Overall	24934	137	2	1.46%	26160	59	10	16.95%	51094	196	12	6.12%

**Table-3: Characteristics of VL deceased confirmed by verbal autopsy**

	VL deceased; n (%)		
	Male N=9	Female N=3	Overall N=12
Age group			
<17 years	4 (44.4)	2 (66.7)	6 (50.0)
17-45 years	5 (55.6)	1 (33.3)	6 (50.0)
>45 years	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity			
Tribal	8 (88.9)	2 (66.7)	10 (88.3)
Bangali	1 (11.1)	1 (33.3)	2 (16.7)
Received treatment before death	5 (55.6)	3 (100.0)	8 (66.7)
Having TB co-infection	0 (0.0)	1 (33.3)	1 (8.3)
Place of death			
Home	7 (77.8)	2 (66.7)	9 (75.0)
Hospital (tertiary)	2 (22.2)	1 (33.3)	3 (25.0)

Table-4: VL death and VL cured households and the bivariate analysis for socio-economic, VL knowledge and health seeking behavior related information

	VL Death HH N=11 n (%)	VL Cured HH N=154 n (%)	P-Value
Study site			
Mymensingh	2 (18.2)	115 (74.7)	<b>&lt;0.0001</b>
Rajshahi	9 (81.8)	39 (25.3)	
Socio economic status			
Illiterate HH head	6 (54.5)	74 (48.1)	0.677
Labor HH head	10 (90.9)	64 (41.6)	<b>0.003</b>
Income about <100 USD	11 (100.0)	101 (65.6)	<b>0.017</b>
Precarious house	10 (90.9)	83 (53.9)	<b>0.024</b>
Living room with <2	7 (63.6)	67 (43.5)	0.223
Family size with <5 members	2 (18.2)	57 (37.0)	0.331
Having bed-nets	11 (100.0)	98.7 (152)	1.00
Having domestic animals	10 (90.9)	130 (84.4)	1.00
Knowledge about VL			
Symptoms	11 (100.0)	136 (88.3)	0.611
Transmitted by mosquito/sand fly	6 (54.5)	71 (46.1)	0.588
The disease is curable	11 (100.0)	147 (95.5)	1.000
Health seeking behaviors			
Visit qualified provider when get any sick	1 (9.1)	7 (4.5)	0.431
Visit qualified provider when get VL	7 (63.4)	142 (92.2)	<b>0.013</b>
Ethnicity			
Bangali	2 (18.2)	127 (82.5)	<b>&lt;0.0001</b>
Tribal	9 (81.8)	27 (17.5)	

HH refers household

**Table-5: Independent risk factor on visceral leishmaniasis death (OR adjust using stepwise logistic regression)**

Variable	VL death HH	VL cured HH	Odds ratio	(95% CI)	Adjusted odds ratio <sup>s</sup>	(95% CI)	P- value
Ethnicity							
Tribal	9	27	21.2	(4.3 –103.5)	18.1	(3.6–90.6)	<0.0001
Bangali	2	127	1.00		1.00		
VL health seeking behavior							
Unqualified doctor	4	12	6.8	(1.7–26.4)	4.3	(1.00–20.5)	0.063
Qualified doctor	7	142	1.00		1.00		

*HH refers household*

*<sup>s</sup> adjusted by study location, household head occupation, income, housing structure*

**Figures**

*Figure-1: Study profile*

*Figure-2: study area map including spatial distribution of households, households with VL and VL death during August 2009 – December, 2011*

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## Visceral leishmaniasis associated mortality in Bangladesh: A retrospective cross-sectional study

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# Visceral leishmaniasis associated mortality in Bangladesh: A retrospective cross-sectional study

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## Abstract

**Objective:** To investigate the actual visceral leishmaniasis (VL) mortality and its risk factors in the two VL endemic regions in areas of Bangladesh

**Design:** Retrospective cross sectional

**Setting:** Two geographically and culturally different visceral leishmaniasis VL endemic sub-districts, Godagarai under in the district of Rajshahi District and Trishal under in the district of Mymensingh District in Bangladesh, August 2009 — December, 2011

**Participants:** 51094 inhabitants from randomly selected two Unions in the two sub-districts.

**Main outcome measures:** VL Death by visceral leishmaniasis as reported by the family members was confirmed independently by three expert qualified physicians independently by using the Verbal Autopsy procedure ICD10 guideline.

**Results:** A-The total number of 12032 households were studied, with a population of people screened for VL death was 51094 from 12031 households inhabitants, where 26160 inhabitants (6566 households) were from the Rishikul Union under from Godagari and Trishal Subdistrict, Rajshahi. About 16% of the people from Godagari, were tribal. The average age of the study population was 25.6 years (SD, 18.4) and 49.7% were female. VL case fatality rate averaged 6.12% (12/196) including was about 1.5% (2/137) in Mymensingh whereas it was about 17.0% (10/59) in Rajshahi Godagari. Most of the VL deaths (9/12, 75%) occurred at home and rest in tertiary hospitals. None of these deaths had been reported in the national VL surveillance system. Visceral leishmaniasis VL case fatality rate in the Tribal ethnic (22.2%) population was about 17 times higher than the Bangali ethnic (1.3%) population (P<0.0001). About 75% (9/12) visceral leishmaniasis diseased died at home. The households with Tribal ethnicity was had 18 times (OR=18.1, 95% CI, 3.6-90.6) higher risk of getting visceral leishmaniasis for VL death than the households with compared to Bangali ethnicity (P<0.0001).

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**Conclusion:** ~~Visceral leishmaniasis~~VL death were found to be high in the study areas and was underreported. ~~mortality is high at the community and the~~The Tribal ethnic population ~~is was~~ at highest risk for ~~visceral leishmaniasis~~VL death. The national ~~visceral leishmaniasis~~VL elimination program should give special attention to the tribal community in the ~~visceral leishmaniasis~~-endemic areas specially for those in Godagari, Rajshahi and in Bangladesh and the existingshould strengthen VL surveillance systems ~~needs to be improved by integrating active case detection and active follow up of the treated patient's~~including tertiary hospitals in the National surveillance system.

**Key words:** Visceral leishmaniasis, Mortality, Verbal Autopsy, Tribal, Bangladesh

## Strength and limitation of the study

### Strength

- This is the first study in the South East Asia Region, in which ~~we investigated the~~ VL related mortality was investigated in Bangladesh using the verbal autopsy procedure.

### Limitation

- The study is limited to only two unions of endemic districts.
- The recall bias in the study cannot be excluded, but we tried to minimize ~~it as much as possible~~ this by probing with different events occurred during last 2 years from the date of interview

## Introduction

Leishmaniasis one of the most important vector-borne diseases with an estimated 1.98 million disability adjusted life years and 20000 to 40000 deaths per annum<sup>12</sup>. Recent empirical estimates ~~s show found theat~~ annual incidence of worldwide about 0.2 to 0.4 and 0.7 to 1.2 million Visceral ~~H~~ Leishmaniasis (VL) and Cutaneous ~~H~~ Leishmaniasis (CL) to be 0.2-0.4 and 0.7-1.2 million cases ~~occurred~~ respectively ~~each year~~<sup>1</sup>. Ninety percent of the global burden of VL ~~is found occurred in six countries~~, India, Bangladesh, Sudan, South Sudan, Brazil and Ethiopia<sup>1</sup>. There are an estimated population at risk for VL is 200 million ~~population at risk~~ in the Indian subcontinent, ~~with and annual incidence of which reports~~ 25 000 to 40 000 ~~eases~~ and number of death about 200-300 ~~deaths every year~~<sup>3</sup>. For many years, there has been a substantial number of VL cases that have never been reported due to lack of proper surveillance systems which ~~make contributes to~~ the ~~disease~~ neglected of this disease. In Bangladesh, VL re-emerged in the early eighties and since then there has been more than 90000 ~~VL~~ cases have been documented<sup>4,5</sup>. Since 1996 ~~the~~ reported VL incidence in Bangladesh has range ~~ds~~ from 7000-9000 cases per year ~~since 1996 and but this~~ is likely to be significant underestimated<sup>6</sup>. After adjusting the substantial under reporting factor, the recent estimated VL incidence in Bangladesh ranges from 12400-24900 cases per year<sup>1</sup>. The disease ~~affects about is prevalent in~~ 45 districts ~~in of~~ Bangladesh, however most of the cases are reported from the Mymensingh District<sup>4,5</sup>. The female *Phlebotomas argentipes* sand fly is the only vector; humans are the only reservoir and *Leishmania donovani* is the only species responsible for VL in the Indian subcontinent, including Bangladesh<sup>3-5</sup>. The disease is fatal if not treated. Even with treatment the mortality rate is high (10%)<sup>7</sup>. In 2005, a national VL elimination program has been launched jointly by the Health Ministries from Bangladesh, India and Nepal to eliminate VL by 2015<sup>8</sup>. In Bangladesh ~~the~~ goal of the elimination program is to reduce VL cases below 1 per 10,000 people in the VL endemic sub-districts (known as Upazila) areas<sup>8</sup>. The strategies for VL elimination includes through active case detection, ~~proper management of cases~~ of VL and Post-kala-azar Dermal Leishmaniasis (PKDL) cases, adequate treatment of VL and PKDL cases, and interruption of disease transmission through integrated vector management ~~strategies~~, and social mobilization<sup>8,9</sup>.

To support the national elimination program in Bangladesh Since 2006, several operational research programs activities have been conducted since 2006 by government and non-government partner organizations to support the national elimination program in Bangladesh. These research findings programs revealed that the passive case detection (existing surveillance system) highly under estimated VL cases compared to

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~~active case detection~~ in Bangladesh<sup>10-12</sup>. ~~The~~ In 200, a study conducted in the Rajshahi District ~~also~~ showed that the incidence of VL was 27 higher than the elimination target ~~in 2008~~. It also found that ~~and~~ the knowledge of the community people about VL disease and, its vectors was poor and their health seeking behavior was also poor unsatisfactory.<sup>12</sup>

Similar to VL case reporting, it can be assumed that the mortality rate of VL is also highly underestimated in Bangladesh. Until now, there is no well designed study to measure ~~actual~~ VL mortality in highly VL endemic areas of Bangladesh. According to the Directorate General of Health Services, the reported annual number of VL deaths varied from 6 to 36 during 1999-2009<sup>13</sup>, ~~which~~ This seems appears to be highly under estimated, because a as compare to a small area community based study in a small endemic area which reported a high VL mortality rate (about 10.0%) in 2003<sup>14</sup>. The possible reason for the highly underestimation of VL death ~~reporting in Bangladesh~~ might be ~~because of a~~ shortfall in the passive the reporting system which does not include tertiary hospitals under VL case surveillance. ~~It is most likely that~~ VL patients who are poor and living in remote communities far from health care facilities often die at home without seeking treatment. ~~Another important cause of underestimation of VL deaths is that patients from tribal community don't seek medical care at the hospital due to cultural beliefs and prefer to stay home or go to the or preferred~~ traditional healers for their health care and ~~die at home~~ do not report to the public health facilities. Underestimation of deaths contributes to VL remaining a major neglected tropical disease. These points are not considering in the existing surveillance system in Bangladesh which makes VL a neglected disease due to its low mortality rate as reported by existing passive surveillance. Thus, there is a need to investigate the magnitude of VL deaths and its risk factors through a well design study and using adequate tools for investigation of death. mortality rate by VL through active surveillance.

Culturally, autopsy is not well accepted in Bangladesh. ~~However v~~ Verbal autopsy (VA) could be the alternative since it is the best available approach for assessing causes of death in communities where most deaths occur at home <sup>[7]</sup>. ~~There has been~~ Until now no study has been conducted to ~~date to~~ investigate the actual VL mortality in the Indian subcontinent including Bangladesh after the start of VL elimination program.

We have therefore undertaken this study to fill this knowledge gap in Bangladesh. The objective of ~~our~~ this study is to estimate the actual VL mortality and risk factors in two geographically and culturally different highly VL endemic ~~regions-areas in of~~ Bangladesh.

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# Methods

## Study sites and population

The study was carried out in two different VL endemic areas of Bangladesh: Upazilas (Godagari sub-  
districts) in the district of the Rajshahi and the Trishal sub-district in the Mymensingh and Godagari  
from July 2011 to December 2011 district. Both Trishal and Godagari are highly endemic for VL. The  
study activities was performed from July 2011 to December 2011. Mymensingh district reports more  
than 60% of the total VL cases in the country<sup>5</sup>. The Trishal Upazila is one of the five most VL endemic  
sub-districts in Mymensingh and is located at 24.5792742°N 90.3950388°E under the Mymensingh  
District, which is about 120 km north of the capital city, Dhaka of Bangladesh. The Upazila Trishal  
consists of 12 unions parishads and 160 villages and all the unions are endemic for VL. Another study  
Upazila, Godagari is one of the highest VL endemic sub-district in Rajshahi which is located at  
24.4667°N 88.3306°E under the Rajshahi District in the north-western part of Bangladesh. This  
Upazila consists of with nine 9 unions parishads and 396 villages and has a significant with different  
ethnic Tribal populations. Godagari was included in the study was to investigate the VL death among  
Tribal populations and to compare it with that of the Bangali ethnic population. Two Unions from these  
Upazilas were included in the study where all the households were enrolled after obtaining written  
consent from the head of household Based on our past experience, we assumed that Tribal population  
was at higher risk for VL deaths.

## Sample size estimation

It was reported that the VL case fatality rate was about 10% in 2003 in VL endemic areas in Mymensingh  
District<sup>14</sup>. We assumed significant reduction of case fatality rate alonge with the reduction of VL  
incidence as a benefit of VL elimination program in Bangladesh which has been launched in 2006.

We therefore ~~The sample size has been~~ calculated the sample size assuming an average of 6.5% VL case fatality rate (CFR) in the endemic areas in Bangladesh. To demonstrate the VL case fatality rate of 6.5% with  $\pm 3.0\%$  precision and 95% confidence interval (CI), a total of 191 VL case was needed to obtained a 6.5% CFR from in the study areas. To obtain a minimum of 191 past VL cases in the last 2 years, the survey required a total of 47750 people (considering annual VL incidence 20 per 10000). Assuming an annual VL incidence of about 10 per thousand population in the endemic areas, a minimum of 19,100 population was required for the study. We The study areas included a population of 51094 ( studied a population of 24934 from Trishal Upazila and 26160 from Godagari Upazila (a total of 51094 population) which gave sufficient power to the study.

## Study design and sampling

The study design was retrospective cross sectional. ~~Two study arms were identified firstly, one was As mentioned above, we selected Trishal and Godagari Upazila from the Rajshahi District with a tribal ethnic community and another was the Trishal Upazila from the Mymensingh District without any Tribal ethnic community. There were five VL endemic Unions out of nine Unions in Godagari whereas all 12 Unions in Trishal were endemic for VL. For each Upazila, sub-district and one endemic Union from each sub-district was selected taken randomly from all the endemic Unions in the corresponding Upazilas for the study (Figure 1). Before starting the survey, Field Research Assistants (FRAs) were trained on data collection procedures. The trained field research assistants (FRAs) visited each household, made household rosters and in the study area and collected socio-demographic information from all family members after obtaining written consent from the head of the household head. During their visit, they FRA also identified households with past history cases of VL, any death as well as and suspected VL death within the last two years. To minimize recall bias, the FRAs used probing with different events (mainly religious festivals) occurred during last 2 years from the date of interview. We defined a suspected VL death as a death with a history of VL treatment or a death with an illness associated with two or more weeks of fever, plus at least one of the following: weight loss, enlarged abdomen abdominal fullness, abdominal pain, and/or skin darkening. Then the VA method was applied to confirm the suspected VL death (please see below). The household with experience of VL death confirmed by VA was defined defined as VL death households. Households with a past history of VL but no deaths in last two years was defined as a VL cured household (Figure-1). Household heads from both the VL death and VL cured households were interviewed by the FRAs with a structured questionnaire for collection of information about the household's to determine their socio-economic status; knowledge concerning about VL and its vector, and for information about the treatment seeking behavior used. At the same time, the coordinates (longitude and latitude) of all the households in the study area were recorded using eTrex Venture Garmin single handheld GPS receivers.~~

## Verbal Autopsy at suspected VL death household

We developed the interview questionnaire for VA followed by an ICD 10 VA guideline and the questionnaire was reviewed by a VL expert. We also translated the questionnaire into local language which has been further reviewed, revised and approved by the icddr,b Ethical Review Committee. Briefly, the tool assessed the identity of the deceased and established the sequences of the events leading to death including signs and symptoms of the illness before death. The FRAs identified the suspected household with a VL death within the last 2 years since the suggested timing for  
It is recommended that VA ~~is~~ should be done within 3 months to 2 years to minimize the recall bias<sup>15</sup>. After identifying the household with a suspected VL death, a VL expert physician visited the household immediately ~~along~~ with a FRA ~~to confirm whether the death was due to VL by using~~ and conducted the VA ~~method. We developed the interview questionnaire for VA followed by an ICD 10~~

verbal autopsy guideline and the questionnaire was reviewed by VL expert. We also translated the questionnaire into local languages for the interviews which has been further approved by the IRB, icddr, Bangladesh. In short, the tool assessed the identity of the deceased and established the sequences of the events leading to death including signs and symptoms of the illness before death. Respondents for the interview were household head/ close relatives. Studies with VA, since experience shows that close relatives rarely refuse to give information and, with some survey situation response rate were reporting 100% ~~response rates~~<sup>16-18</sup> ~~Before going to interview, the aim of the study was clearly explained and informed consent was obtained from the respondent.~~ Another second VL specialized expert physician with local experience independently reviewed each VA questionnaire independently and indicated whether the cause of death was VL or not. In case of disagreement between first and second physician, the VA questionnaires were reviewed by a third expert physician, and his verdict was final.

### Statistical analysis

All data was entered and stored in a well checked data entry program developed by EPI Info software (Centers for Disease Control and Prevention, Atlanta, GA). Data was cleaned and checked for duplicates. We explored ~~Descriptive statistics are explored~~ to consider the nature of data. We calculated CFR and compared the rates between different study sites (Godagari versus Trishal) and ethnic groups (Tribal versus Bangali) with the Z-test. ~~Comparison of outcome variable distribution between VL death and VL cured household has done using parametric and non-parametric approaches, where applicable.~~ Socio-economic, knowledge about VL and health seeking behavior of each household head related variables were dichotomized before including in bivariate analysis. Variable significant ( $P \leq 0.05$ ) associated with outcome VL death household in the bivariate analysis (Pearson's chi square and Fisher exact tests, where applicable) were included in a logistic regression procedure model. The final model was obtained by a backward selection strategy recommended by Kleinbaum et al.<sup>19</sup>.

The ~~analysis was carried out using the~~ statistical software SPSS 13.0 for windows (SPSS, Chicago, IL, USA) ~~was used to carry out all the analysis. We constructed t~~The study area map with spatial distribution of households in the study areas was created by using ArcView GIS version 3.2 (ArcGIS, ESRI, USA).

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Results

Socio-demographic characteristics of the study population

A total of 51094 population-people (12032 households) were studied where 26160 population- (6566 households) came from the Rishikul Union under, in the sub-district of Godagari, in the district of Rajshahi and rest of the people from Sakhua Union in the sub-district of Trishal in the Mymensingh district. Average age of the study population was 25.6 years (SD, 18.4) and 49.7% were female (Table-1). About 16 % (n=4243) of the population was tribal in Godagari whereas all the people are non-tribal (Bangali ethnicity) in the Trishal area (Table-1).

VL-associated mortality based on verbal autopsy

During the period August 2009 — December, 2011, it was found that VL affected 0.4% (n=196/51094) of the people in the study areas. The proportion of VL affected population was higher in Trishal VL occurred out of the total population in the study areas during August 2009 — December, 2011, where (0.5 % (n=137/24934) were found in the Trishal Upazila and compared to Godagari (0.2 % (n=59/26160) in the Godagari Upazila. Trained FRAs suspected a total of Twenty-five suspected 25 VL death and VL expert physicians confirmed VL deaths in 12/25 by VA was identified in the household survey by FRAs. The VL CFR in two areas averaged 6.12% (12/196) and accounted for 3.14% total deaths in the study areas. Among them, 10 and 2 The VL deaths (in total 12) were confirmed by VA which corresponds The VL CFR differed significantly from Godagari than Thrishal and was 17.0% (12/59) and 1.5% (2/137) case fatality rate (CFR) for Godagaria Upazila and Trishal Upazila respectively (P<0.0001) (Table-2). Significant, a VL CFR difference was observed between the Godagari and Trishal Upazila (16.95 Vs 1.46, P<0.0001). VL CFR in the Tribal (22.2%) population (22.2%) is was about 17 times higher than the nontribal/Bangali ethnic (1.3%) population (P<0.0001).

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5 It was also found that VL proportionate death accounted for 3.0% (12/382) of the total deaths in the  
6 study areas. About six percent of CRF was found as an overall estimate of Godagari and Trishal study  
7 areas. Group specific as well as overall CFR are presented in the Table 2.  
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11 Among 12 confirmed VL deaths, 50% ( $n=6/12$ ) were children aged below 17 years and 75% were male  
12 ( $n=9/12$ ). Most of the deaths occurred in tribal ethnic populations which accounted for 88.3% (10/12) of  
13 total death. About ~~thirty three percent~~ 33% (4/12) of all confirmed deaths didn't receive ~~any~~ treatment  
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illness that led to death. Tuberculosis as an associated illness was found in eight percent (1/12) of the deceased. The majority of the deaths occurred at home and rest were in the tertiary hospital (Table-3). When checked for reporting of these 12 VL deaths in the existing VL surveillance system, none were recorded. The ~~S~~patial distribution of households with VL and VL death during August 2009 — December, 2011 are shown in the figure 2.

**Factor associated with the VL death**

To identify factors associated with VL death households, we compare household related information between 11 VL death households and 154 VL cured households. Bivariate association showed that households with a VL death significantly defer between Tribal-ethnic and Bengali ethnic groups (P<0.0001). The VL death households were socio economically poorer than VL cured households ~~as demonstrated by~~ significantly ~~difference observed on~~ more labor occupation of household head ~~occupation, less monthly~~ income and more poor housing structure in VL death households (Table-4). The level of knowledge ~~was~~ about VL was however almost the same between the two groups ~~as no significant association found in bivariate analysis~~. Although general health seeking behavior of VL death and VL cured household was the same (P=0.431), ~~however their~~ VL health seeking behavior differed significantly ~~between these two groups~~ (P=0.013) (Table-4). About 96% (142/154) of VL cured households visited qualified doctors when anyone in the family had VL whereas only 63.4% (n=7/11) of VL death households visited qualified doctors for the same. ~~Through the use of T~~he logistic regression model showed that, only the ethnicity was identified as ~~an the only~~ independent risk factor associated with for VL death households. The ~~Aa~~adjusted model showed that households s of Tribal-ethnicity were ~~as~~ at 18 (OR=18.1, 95% CI, 3.6-90.6) times higher risk of having a VL death than household with Bengali-ethnicity (P<0.0001) (Table-5).

**Discussion**

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Our study is the first study to estimate the actual mortality of VL in Bangladesh through the VA, and the major findings for the study ~~is-are: VL mortality in the endemic community remain high, that VL mortality in the endemic community is higher than previously thought. Our study also suggests that the Tribal population are at high risk of VL death since VL mortality of the tribal population in Rajshahi is very high compared to the most endemic district of Mymensingh, which contributes about 60% of the national VL disease burden<sup>5</sup> and there is underreporting of VL deaths by the existing VL surveillance system.~~ The findings of our study is very important for the national VL elimination program in terms of making more effective program planning to achieve the elimination goal in Bangladesh.

**Comparison with other studies**

It is alarming that the case fatality rate is very high in the Tribal community in Rajshahi which was found to be about 22%~~(10/45)~~. The probable cause of the high VL CFR in that community could be their poor health seeking behaviors as they rarely visit government hospitals due to cultural believes and prefer traditional healers<sup>20</sup>. As a result, VL patients in that community remain untreated and die at home. We found that about 33%~~4 out of 12~~ confirmed VL deaths ~~(about 33%)~~ were not treated before dying and all the untreated belonged to the Tribal community in Rajshahi. A previous study<sup>12</sup> conducted at the same community also identified a lack of access to proper health care, including high delay in VL diagnosis and treatment. Although Mymensingh is highly endemic for VL, the CFR of VL patients living in Mymensingh (all are Bangali enthnic) was not as high as the CFR in Rajshahi district. Additionally, we found low VL mortality in Mymensingh as compared to the reported VL mortality in 2003<sup>14</sup>. The present VL mortality in Mymensingh could be due to the attention of this highest endemic area by the national VL elimination program ~~in Bangladesh of the country.~~

The hospital based VL CFR is substantially under estimated in the Indian subcontinent, including Bangladesh<sup>1</sup>. In Bangladesh, the existing hospital based surveillance system is mainly based on the passive reporting system. There is no active follow-up of the VL patients who completed the treatment at the hospital. As a result, the patients who died at the community/home are missed by the existing

surveillance systems. Until recently, the tertiary hospitals did not report VL cases to the national program. Even very recently only two tertiary hospitals started reporting of VL cases to the national surveillance system. Our study results complied with these facts. Forty two percent (5/12) of VL death occurred at home although they had been treated in the hospitals. Twenty five percent (3/12) died in the tertiary hospitals and test 33% (4/12) died at home without treatment. ~~Our study revealed that 4 (50%) died at home out of 8 VL deaths who received treatment at the hospital before death. The other four died at home without treatment at the hospital.~~ It is surprising that none of these 12 VL deaths were reported by the VL national program even when the deaths occurred in the tertiary hospital. Thus VL deaths are highly under reported. Therefore ~~it is important to~~ there is an urgent need for improvement of the existing surveillance system, ~~by integrating implementation of active case detection as well as the active follow up for the surveillance of~~ VL patients under treatment and inclusion of the tertiary hospitals (especially those in the VL endemic areas) under a routine VL case reporting mechanism. ~~who are admitted to the hospital for treatment.~~ Another important finding of the study is that about ~~eight percent (1/12)~~ 8% of VL deceased had tuberculosis which indicates the existence of VL-Tuberculosis co-infection in VL endemic areas in Bangladesh. The evidence of VL associated with tuberculosis has been reported in several VL endemic countries, including India <sup>21</sup>. However this type of data has not been previously reported from Bangladesh.

Although there are previous reports <sup>22-24</sup> ~~about on~~ clinical risk factors for VL death, so far our study is the first where household level risk factors were explored. The households with VL deaths were found to be socio economically poorer than households without VL deaths. ~~Also~~ Moreover poorer VL health seeking behavior was observed in the households with VL deaths. Tribal households s was the only independent dominating risk factor of having a VL death as determined by the adjusted regression model. This is because the tribal ethnic populations are comparatively poorer, less educated and less aware about health care compare to the Bengali ethnic population. The VL elimination program should therefore take necessary actions to improve the VL health seeking behavior of the tribal population especially those in the Rajshahi VL endemic areas to minimize their risk from VL death.

## Strength and limitation of the stud

This is the first study in the South East Asia Region, in which we investigated the VL related mortality in Bangladesh using the VA verbal autopsy procedure. However, the study is however limited to only two unions of endemic districts. The recall bias in the study cannot be excluded, but we tried to minimize it as much as possible by probing with different events occurred during the last 2 years from the date of interview.

## Conclusion

Our study highlights ~~eds that~~ VL mortality in two VL endemic areas of Bangladesh, underlined underreporting of VL deaths and found is high in the community and tribal ethnic populations ~~are~~ at higher risk for VL death. A substantial number of VL patients never visit hospital for proper health care and die at home. The national VL elimination program should give special attention to the tribal community in the VL endemic areas of Bangladesh and the existing surveillance systems ~~needs to~~ must be improved by integrating active case detection as well as the active follow-up of the treated patient's.

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**Contributions**

MMH, and DM Conceived and design the study. MMH, RC, APD, S KB and DM wrote the paper; MMH performed the statistical analysis, DG participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript. MMH is the study guarantor.

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## Competing interests

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

## Ethical Approval

The study was approved by the institutional Ethical Review Committee of icddr,b, Dhaka, Bangladesh (Research Protocol # PR-11027). All households in the study areas were enrolled in the study after obtaining written consent from the head of the household. Informed consent was obtained from the respondent (head of household/close relatives) before conducting verbal autopsy.

## Transparency

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained

## Data Sharing

No additional data available.

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**What is already known to this topic**

The case fatality rate was 1.5% and about 10.0% respectively by WHO estimates based on hospital-base surveillance from 2004 to 2008 and from a community based study conducted in 2002-2004. In the study the case fatality rate of VL was related with gender.

**What this study adds**

The VL case fatality rate was unknown after introduction of the VL elimination program. ~~Current~~ This study showed that the overall case fatality rate was 6.12% in two VL endemic areas which is considered ~~still~~ high. The VL deaths were under reported. The tribal populations are highly vulnerable to VL death (~~CRFCFR~~, 22.2%). Tuberculosis as co-infection also contributed to VL related death.

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Tables

Table-1: Socio-demographic characteristics and history of VL and death in the study population

	Trishal, Mymensingh	Godagari, Rajshahi	Total
Total Population	24934	26160	51094
Total household	5466	6566	12032
Mean Age (SD)	24.53 (18.91)	26.70 (17.92)	25.65 (18.44)
Age ratio			
<17 years	10868 (43.6)	9309 (35.6)	20177 (39.5)
17-45 years	10091 (40.5)	12895 (49.3)	22986 (45.0)
>45 years	3975 (15.9)	3956 (15.1)	7931 (15.5)
Male population	12958 (52.0)	13267 (50.7)	26225 (51.3)
Ethnicity			
Bangali	24934 (100.0)	21917 (83.8)	46851 (91.7)
Tribal	00 (0.0)	4243 (16.2)	4243 (8.3)
Past h/o VL in last 2 years	137 (0.5)	59 (0.2)	196 (0.4)
Total death reported by respondent in last 2 years	208	174	382
Total suspected VL death in last 2 years	3	22	25
Total VL death in last 2 years confirmed by VA	2	10	12

Table-2: Visceral leishmaniasis cases and mortality in Bangladesh, August 2009 — December, 2011

	Trishal, Mymensingh				Godagari, Rajshahi				Overall			
	Population	VL case	VL death	Mortality	Population	VL case	VL death	Mortality	Population	VL case	VL death	Mortality
<b>By sex</b>												
Female	11976	50	1	2.0%	12893	22	2	9.09%	24869	72	3	4.17%
Male	12958	87	1	1.15%	13267	37	8	21.62%	26225	124	9	7.26%
<b>By age</b>												
Child	11091	74	0	0.0%	9687	30	6	20.0%	20778	104	6	5.77%
Adult	13843	63	2	3.17%	16473	29	4	13.79%	30316	92	6	6.52%
<b>By ethnicity</b>												
Tribal	0	0	0	0.0%	4243	45	10	22.22%	4243	45	10	22.22%
Bangali	24934	137	2	1.46%	21917	14	0	0.0%	46851	151	2	1.32%
<b>Overall</b>	24934	137	2	1.46%	26160	59	10	16.95%	51094	196	12	6.12%

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Table-3: Characteristics of VL deceased confirmed by verbal autopsy

	VL deceased; n (%)		
	Male N=9	Female N=3	Overall N=12
Age group			
<17 years	4 (44.4)	2 (66.7)	6 (50.0)
17-45 years	5 (55.6)	1 (33.3)	6 (50.0)
>45 years	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity			
Tribal	8 (88.9)	2 (66.7)	10 (88.3)
Bangali	1 (11.1)	1 (33.3)	2 (16.7)
Received treatment before death	5 (55.6)	3(100.0)	8 (66.7)
Having TB co-infection	0 (0.0)	1 (33.3)	1 (8.3)
Place of death			
Home	7(77.8)	2(66.7)	9 (75.0)
Hospital ( <a href="#">tertiary</a> )	2(22.2)	1(33.3)	3 (25.0)

**Table-4: VL death and VL cured households and the bivariate analysis for socio-economic, VL knowledge and health seeking behavior related information**

	VL Death HH N=11 n (%)	VL Cured HH N=154 n (%)	P-Value
Study site			
Mymensingh	2 (18.2)	115 (74.7)	<b>&lt;0.0001</b>
Rajshahi	9 (81.8)	39 (25.3)	
Socio economic status			
Illiterate HH head	6 (54.5)	74 (48.1)	0.677
Labor HH head	10 (90.9)	64 (41.6)	<b>0.003</b>
Income about <100 USD	11 (100.0)	101 (65.6)	<b>0.017</b>
Precarious house	10 (90.9)	83 (53.9)	<b>0.024</b>
Living room with <2	7 (63.6)	67 (43.5)	0.223
Family size with <5 members	2 (18.2)	57 (37.0)	0.331
Having bed-nets	11 (100.0)	98.7 (152)	1.00
Having domestic animals	10 (90.9)	130 (84.4)	1.00
Knowledge about VL			
Symptoms	11 (100.0)	136 (88.3)	0.611
Transmitted by mosquito/sand fly	6 (54.5)	71 (46.1)	0.588
The disease is curable	11 (100.0)	147 (95.5)	1.000
Health seeking behaviors			
Visit qualified provider when get any sick	1 (9.1)	7 (4.5)	0.431
Visit qualified provider when get VL	7 (63.4)	142 (92.2)	<b>0.013</b>
Ethnicity			
Bengali	2 (18.2)	127 (82.5)	<b>&lt;0.0001</b>
Tribal	9 (81.8)	27 (17.5)	

*HH refers household*

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Table-5: Independent risk factor on visceral leishmaniasis death (OR adjust using stepwise logistic regression)

Variable	VL death HH	VL cured HH	Odds ratio	(95% CI)	Adjusted odds ratio <sup>s</sup>	(95% CI)	P- value
Ethnicity							
Tribal	9	27	21.2	(4.3 –103.5)	18.1	(3.6–90.6)	<0.0001
Bangali	2	127	1.00		1.00		
VL health seeking behavior							
Unqualified doctor	4	12	6.8	(1.7–26.4)	4.3	(1.00–20.5)	0.063
Qualified doctor	7	142	1.00		1.00		

HH refers household

<sup>s</sup> adjusted by study location, household head occupation, income, housing structure

## Figures

*Figure-1: Study profile*

*Figure-2: study area map including spatial distribution of households, households with VL and VL death during August 2009 — December, 2011*



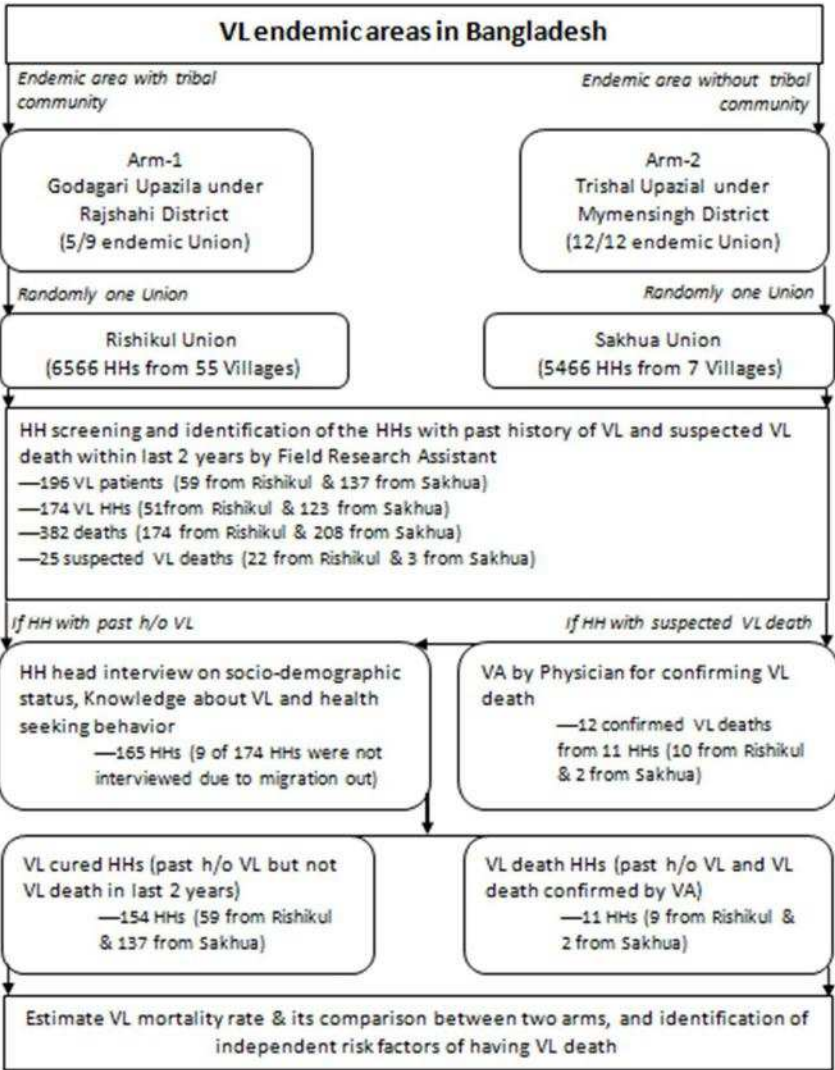


Figure-1: Study profile

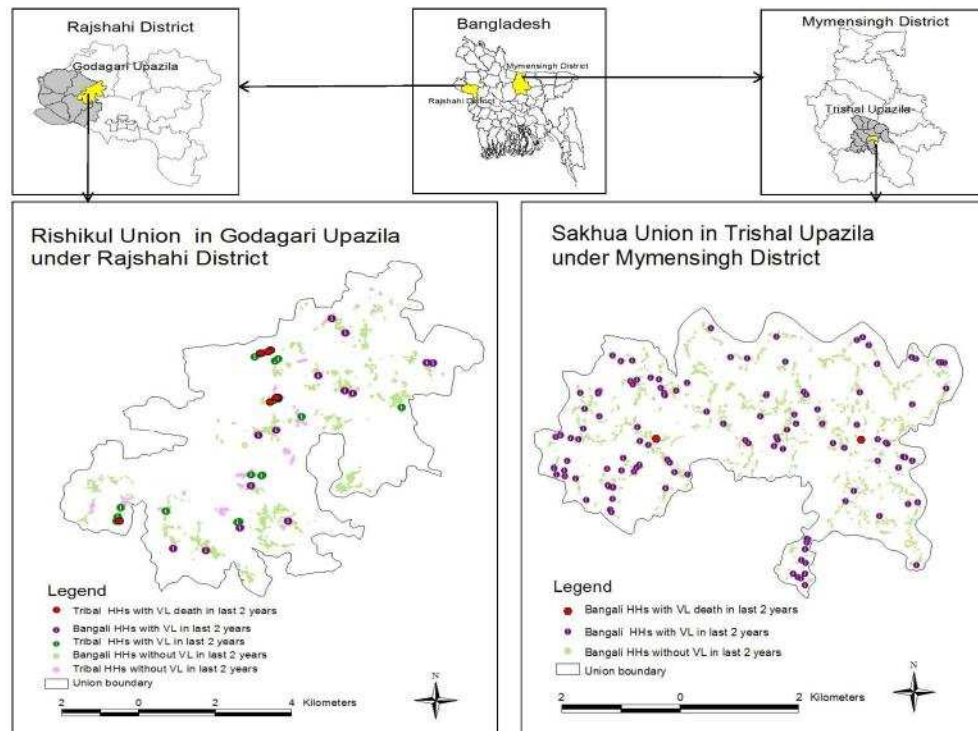


Figure-2: study area map including spatial distribution of households, households with VL and VL death during August 2009 - December, 2011  
714x535mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Checklist
Title and abstract	1	(a) Done, see "Title" (b) Done, see "Abstract"
<b>Introduction</b>		
Background/rationale	2	Done, see "Introduction"
Objectives	3	Done, see "Introduction"
<b>Methods</b>		
Study design	4	Retrospective cross-sectional study. See "Study design and sampling" and Figure 1
Setting	5	Done, see " Study site and population"
Participants	6	(a) Retrospective cross-sectional study — mention in "Study design and sampling" See figure 1
Variables	7	VL death confirmed by verbal autopsy procedure; History of VL in last two years; Socio demographic, Socio-economic and knowledge concerning VL and about treatment seeking behavior.
Data sources/ <sup>8*</sup> measurement		Data were collected by research team from the study areas. See "Method"
Bias	9	Random selection of the study area. See "Figure 1"
Study size	10	Done, see "Sample size estimation"
Quantitative variables	11	Done, see "Statistical analysis"
Statistical methods	12	(a) Done , see "Statistical analysis" (b) Done, see "Statistical analysis" (c) Explain how missing data were addressed, Not applicable <del>Cross-sectional study— Done , see "Statistical analysis"</del> (e) Not applicable
<b>Results</b>		
Participants "Figure -1"	13*	(a) Done , see "Results" and (b) See "Figure-1" (c) See "Figure-1"
Descriptive data	14*	(a) Done , See "Results" and "Table-1" , "Table-2" & "Table-3" (b) Not applicable (c) Not applicable
Outcome data	15*	Not applicable Case-control study—Done see "Results" and "Table-4" Cross-sectional study—Done , see "Results" and "Table-2"
Main results	16	(a) Done , see "Results" and "Table-2" & "Table-5" Not Applicable Not Applicable
Other analyses	17	Not Applicable
<b>Discussion</b>		
Key results	18	Done , see "Discussion"
Limitations	19	Done , see "Discussion"

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Interpretation	20	Done, see "Conclusion"
Generalisability	21	Done, see "Comparison in Discussion"
<b>Other information</b>		
Funding	22	Done, see Funding

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).



HH refers household; VA refers verbal autopsy

Figure-1: Study profile  
146x195mm (300 x 300 DPI)

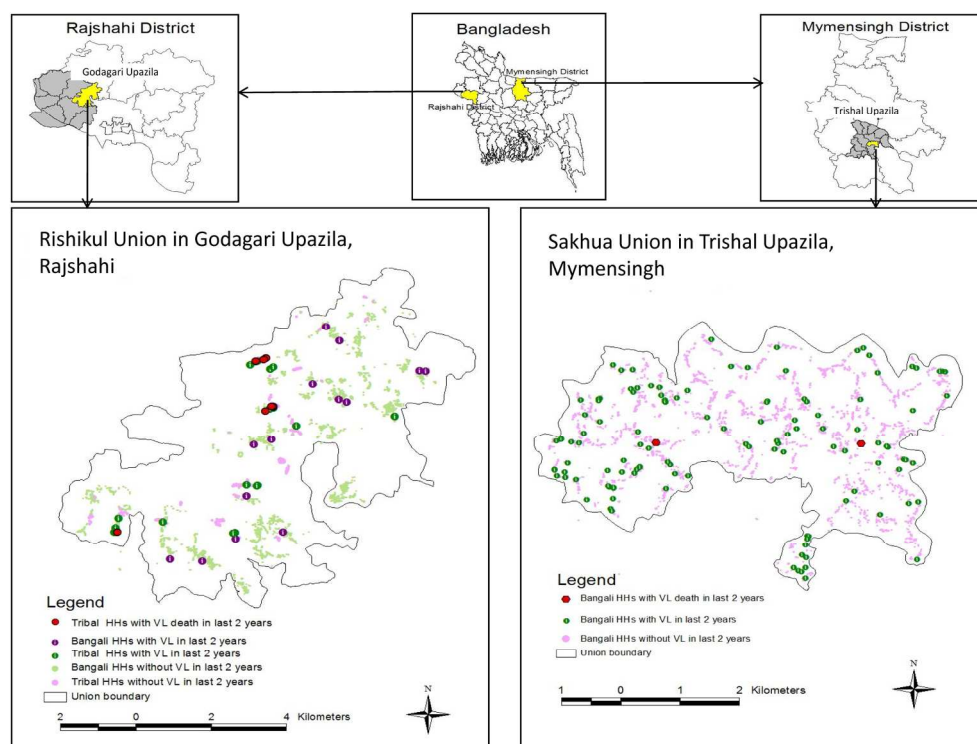


Figure-2: study area map including spatial distribution of households, households with VL and VL death during August 2009 – December, 2011  
173x130mm (300 x 300 DPI)



STROBE Statement—checklist of items that should be included in reports of observational studies

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Statistical methods	12	(a) Done, see “Statistical analysis” (b) Done, see “Statistical analysis” (c) Explain how missing data were addressed, Not applicable <i>Cross-sectional study</i> — Done, see “Statistical analysis” (e) Not applicable
<b>Results</b>		
Participants	13*	(a) Done, see “Results” and “Figure -1” (b) See “Figure-1” (c) See “Figure-1”
Descriptive data	14*	(a) Done, See “Results” and “Table-1”, “Table-2” & “Table-3” (b) Not applicable (c) <i>Not applicable</i>
Outcome data	15*	<i>Not applicable</i> <i>Case-control study</i> —Done see “Results” and “Table-4” <i>Cross-sectional study</i> —Done, see “Results” and “Table-2”
Main results	16	(a) Done, see “Results” and “Table-2” & “Table-5” Not Applicable Not Applicable
Other analyses	17	Not Applicable
<b>Discussion</b>		
Key results	18	Done, see “Discussion”
Limitations	19	Done, see “Discussion”

Interpretation	20	Done, see “Conclusion”
Generalisability	21	Done, see “Comparison in Discussion”
<b>Other information</b>		
Funding	22	Done, see Funding

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