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Urban-rural and sex differentials in tuberculosis mortality in Bangladesh: results from a population-based survey

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Abstract

OBJECTIVE To assess tuberculosis mortality in Bangladesh through a population-based survey using a Verbal Autopsy tool.

METHODS Nationwide mortality survey employing the WHO-recommended Verbal Autopsy (VA) tool, and using InsilicoVA, a data-driven method, to assign the cause of death. Using a three-stage cluster sampling method, 3997 VA interviews were conducted in both urban and rural areas of Bangladesh. Cause-specific mortality fractions (CSMF) were estimated using Bayesian probabilistic models.

RESULTS 6.8% of total deaths in the population were due to TB [95% CI: (5.1, 8.9)], comprising 12.0% [95% CI: (11.1, 12.8)] and 6.42% [95% CI: (5.4, 7.3)] of total male and female deaths, respectively. This proportion was highest among adults age 15–49 years [12.2%, 95% CI: (9.4, 14.6)]. The urban population is more likely to die from TB, and urban males have highest CSMF [13.6%, 95% CI: (9.1, 16.9)].

CONCLUSION Our survey results show that TB is the fifth major cause of death in the general population and that sex and place of residence (urban/rural) have a significant effect on TB mortality in Bangladesh. The underlying causes of higher rates of TB-related deaths in urban areas and particularly among urban males, who have better knowledge and higher enrollment in the DOTS Program, need to be explored.

keywords tuberculosis, mortality, Bangladesh, verbal autopsy

Introduction

Tuberculosis (TB) remains a major public health issue in Bangladesh, and its death toll high. Bangladesh ranks fifth regarding incidence in South East Asia Region and first among the 20 major TB and Multi Drug Resistant (MDR) TB burden countries globally [1, 2]. In 1993, the Government of Bangladesh (GOB) under the National TB control program (NTP) introduced the WHO-recommended strategy of Directly Observed Treatment Short Course (DOTS). The goal was to reduce morbidity, mortality, and transmission of TB until it is no longer a public health problem in Bangladesh [3]. The NTP along with the partners from both public and private sectors have made great efforts to reach the TB control targets linked to the Millennium Development Goals (MDGs) [3].

In 2015, the national estimate of TB incidence and mortality rates were 225/100 000 population and 45/100 000 population, respectively [4]. Bangladesh was marked as one of the 10 countries that contributed to 77% of the globally missing TB cases [4]. The Government Disease Monitoring wing IEDCR reported a high TB prevalence of 295/100 000 population, which nevertheless was much smaller than the previous estimate of 382/100 000 [5].

Before the current survey, we synthesised different databases related to TB mortality, which proved to be insufficient to estimate trends, and effect of age, sex, and area of residence on TB mortality rates in Bangladesh. Of these databases, the sample vital registration system (SVRS) provides cause-specific death rates based on data

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collected by lay reporting, rendering the level of accuracy questionable. Despite this limitation, the SVRS mortality data from 2009 to 2013 showed that TB caused 6% of the total death, of which 65.6% were among males. Furthermore, it revealed that most of the TB deaths had yet not been reported to the NTP.

Goal 3 of the United Nations Sustainable Development Goals (SDGs) aims for ending the TB epidemic by 2030. In this scenario, estimating the impact of programmatic efforts on TB mortality is crucial not only for prioritising TB in the national policy, but also for contributing towards the goals of the global TB strategy.

We conducted a nationwide mortality survey using the WHO-recommended verbal autopsy (VA) tool [6], which is widely used in public health research for assigning cause of death (CoD) in countries with inadequate vital registration (VR) systems [7]. VA is an indirect method to assign CoD based on information on signs, symptoms, and circumstances prior to death obtained from the caregivers of the deceased. It is useful where consistent, timely, and reliable information are not available to estimate the cause-specific mortality in the populations [8].

We aimed to assess the TB mortality situation in Bangladesh with the specific objectives of estimating national and regional (urban/rural) TB deaths, validating the estimates of TB deaths obtained from the analyses of primary and secondary databases, and identifying challenges of using the VA tool in national mortality surveys or the VR system.

Methods

Study design

It was a population-based cross-sectional study of population level causes of death, employing a standard verbal autopsy (VA) tool.

Verbal autopsy tool

We used WHO 2012 VA tool that primarily elicits information on signs, symptoms, medical history, and circumstances preceding death of the individual in the previous 3 years. A standard VA tool includes a VA questionnaire, and classification and diagnostic criteria for assigning CoD. Currently, over 35 demographic surveillance sites in 18 countries including some African countries, India, and China regularly use VA on a large scale [7, 9–13]. In Bangladesh, the WHO recommended VA tool has been used by the International Centre for Diarrheal Disease Research (icddr,b) in the Health and Demographic Surveillance Systems (HDSS) study sites since 2003. icddr,b also used ICD-10 for assigning CoD [13,14]. VA is a useful tool in establishing the probable CoD by interviewing a close caregiver or anyone who can provide witness to the death event [15].

Sampling and sample size

As a part of the national surveillance system, the Bangladesh Bureau of Statistics (BBS) selected 2000 primary sampling units (PSUs) from the country and each of the PSUs consists of about 200 households. In this study, first, a pre-specified number of PSUs were randomly selected from the 2000 PSUs that BBS used for their survey and then all the deaths that occurred about 3 years prior to the survey were identified. A nearest family member or caregiver of the identified deceased was selected to collect information on CoDs (e.g., TB related deaths or deaths due to other causes) using the VA questionnaire.

The recent available estimate of proportion of TB related death 0.085[16] is used to calculate sample size. To detect a significant difference in 20% change in proportion of TB deaths with 80% power at 5% level of significance (two-sided), about 2000 VAs are required. In this study, 4000 VAs are conducted to estimate the proportions of TB related deaths for rural and urban regions, and for male and female with sufficient power. There are eight administrative divisions in Bangladesh, and within each division, there are around ten administrative districts. Dhaka and Chittagong divisions cover the largest geographic area with more than 15 districts, and Sylhet division covers the smallest geographic area with only four districts. A three-stage sampling scheme was used to select PSUs. In stage I, six districts were randomly selected from each division besides Sylhet division where all four districts were selected. In stage II, 570 PSUs were randomly selected from the PSUs within the selected districts. In stage III, seven VAs were randomly conducted from each of the selected PSUs. There were 550–580 VAs interviewed in each division (Figure 1).

Additional VAs were conducted from the nearby locality in cases of insufficient number of deaths in any selected PSUs. VA samples were selected from all deaths (excluding neonate) between June 1, 2013, and May 30, 2016, in the sampled PSUs. The local register of the PSUs maintained by BBS was used to identify the households where the deaths could have occurred in the past 3 years.

Data collection

A Field Data Collection Supervisor (FDCS) and Research assistants (RAs) with a background in health sciences

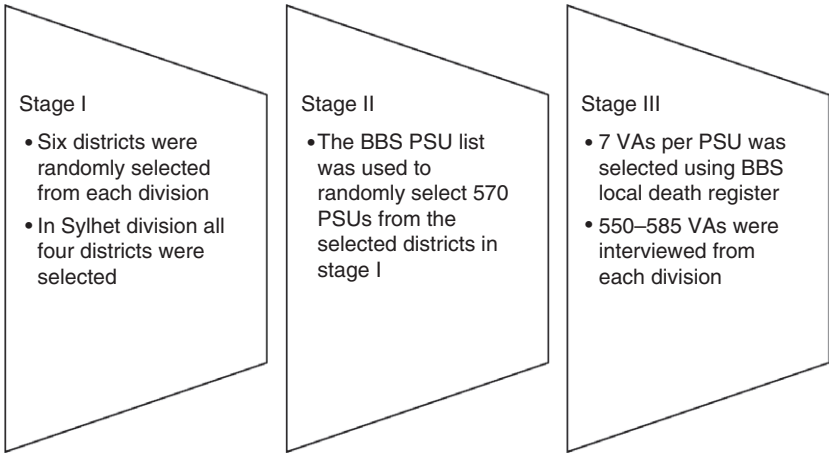

Figure 1 Sampling strategy for three stage sampling.

were recruited for this study. They underwent a rigorous 5-day training on VA tool and interview guidelines facilitated by a team of experts from icddr,b, who have been using the WHO VA tools in their HDSS since 2003. Furthermore, the VA questionnaire was piloted in one PSU outside the sampled PSUs and subsequent de-briefings with feedback, suggestions, and guidance by the principal investigator and co-investigators. It took about 30–60 min to complete one VA interview.

Quality control

Instead of a paper-based tool, an electronic VA tool was used, and field data were entered in tablet computers during the interview to reduce errors. The questions, logical checks, and relevant information were included and coded in the electronic VA questionnaire for the plausibility check. Additionally, the field supervisors provided on-site support to the data collection team for quality assurance. In case of incomplete VA interviews, further efforts were made visiting the same household again to gather complete information. Furthermore, debriefing sessions with the field research team were organised to record their experiences, challenges, comments, or any other information which might influence the quality of the data.

Data management

A database in SQL was developed to enter VA data by the professional data management team for quality purposes. The collected SQL data were extracted from each of the Android tablets using DB Browser for SQLite for 32-bit Windows (version 3.8.0). Extracted datasets were exported as comma-separated (.csv) files and then imported into Stata for Windows (MP, version 13) for cleaning and analysis. Data and field notes were cross-checked to identify any inconsistency in date of birth and age, sex, date of death, date of diagnoses, duration of symptoms, and duplicates. The InsilicoVA requires batch data where each record represents a case consisting binary indicators of presence or absence of a symptom. This file contains 245 fields of symptoms which has been designed to be compatible with the WHO 2012 VA instrument [17]. These batch files were generated using Stata 13 [18].

CoD assignment

To classify the most probable diseases using ICD-10 classification, the InsilicoVA method [19, 20] was used, which employs Bayes' theorem to calculate the conditional probability of each particular CoD given a range of input indicators, such as age, sex, physical signs and symptoms, medical history, and conditions leading to death [14, 19, 20, 23, 24]. CoDs assigned by InsilicoVA are consistent with WHO 2012 VA standard CoD groupings [19,23]. It provides, for each case, up to three possible CoDs or an indeterminate result. If the sum of estimated probabilities of three most likely CoDs is less than 100%, the residual component is assigned as being indeterminate.

Statistical analysis

The general characteristics of the deceased such as age, sex, CoD, and other relevant information are presented in the form of frequency and percentage. The CSMF was determined using InsilocoVA [19], a hierarchical Bayesian model, for inferring individual CoD and population CSMF. The model assumes individual CoD follows a

multinomial distribution and population CSMFs are the corresponding parameters. It was also assumed that the prior distribution of population CSMFs follows a normal distribution and uniform priors were put on the parameters of the normal prior. The posterior probabilities were estimated using MCMC method [19]. All CSMFs and associated 95% credible intervals were obtained using R package InsilicoVA [24]; a multiple linear regression was used to test the significance of the effect of sex, age, and area of residence on proportion of TB death there dependent variable was the estimated individual TB specific mortality fractions and independent variables were sex, age, and area of residence.

Ethical considerations

Ethics approval was granted by the Institutional Review Board of James P Grant School of Public Health, BRAC University, Bangladesh. Authorisation letters were issued by BBS to access the local register prepared for the SVRS. The respondents gave verbal consent and were fully aware of the voluntary nature of the participation. Interviews were conducted in a private setting and information were kept confidential.

Results

A total of 3997 VA interviews were conducted from the randomly selected 570 PSUs in Bangladesh. Among the deaths selected for VA interviews, 3125 (78%) were in rural areas, and 2575 (65%) were males. 142 (4%) of the deaths were children under age five, 84 (2%) of age 5–14 years, 782 (20%) of age 15–49 years, 1056 (27%) of age 50–64 years and rest were older than 65. InsilicoVA determined CoDs for 3976 VA and only 21 (less than 1%) were undetermined. Among the 255 TB deaths 132 (52%) were observed among elderly (age 65+ years), 196 (77%) were males and 193 (76%) were from rural areas.

The mean CSMF of TB (TBCSMF) was 0.068 [95% CI: (0.051, 0.089)]. Thus, at population level, the percentage of TB deaths among total deaths was 6.78 (Table 1), making it the fifth major CoD [rank order (RO) = 5] in Bangladesh. The distribution of CSMFs by sex showed noticeable differences among male and female. The TBCSMF was 0.120 [95% CI: (0.111, 0.128), RO = 3] and 0.064 [95% CI: (0.054, 0.073), RO = 5] for males and females, respectively. 12.0% of male deaths and 6.4% of female deaths were due to TB (Figure 2).

The fit of the multiple regression model of individual level TBCSMF on sex, age-group and region also shows that sex has a significant effect on TBCSMF (P-value < 0.001). The mean difference between TBCSMF of male and female was 0.04 after adjusting for age-group and region (Table 2).

Furthermore, TB was featured in the top five major CoDs for people of age 15 years or older. TBCSMF was highest (2nd Major cause) among people of age 15–49 years, 0.122 [95% CI: (0.094, 0.146), RO = 2]. Among the middle aged (50–64 years) and elderly (65+ years) the TBCSMF was 0.098 [95% CI: (0.082, 0.121), RO = 3] and 0.10 [95% CI: (0.090, 0.112), RO = 5], respectively, i.e., 10.0% of deaths of people age 50 years and older were TB-related (Figure 3).

Although nationally TB was the fifth major CoD, regionally it was the fourth major CoD in both rural and urban areas. Moreover, the distribution of CSMFs showed noticeable differences in regional estimates. The TBCSMF was 0.094 [95% CI: (0.078, 0.116)] and 0.118 [95% CI: (0.103, 0.137)] in rural and urban areas, respectively. Thus, a substantial difference in TB death was observed (rural: 9.5%, urban: 11.9%) in two regions (Figure 4).

In rural areas, among females the TBCSMF was 0.072 [95% CI: (0.060, 0.085), RO = 4] and 0.112 [95% CI: (0.099, 0.126), RO = 3] among males. Hence, among rural females 7.0% and among rural males 8.5% of total deaths were TB-related. In urban areas, TBCSMF among females was 0.051 [95% CI: (0.037, 0.065), RO = 4]

Table 1 Descriptive statistics of top ten cause specific mortality fractions (CSMF)*

Causes of Death (CoD)	CSMF	95% CI	Observed fraction
Stroke	0.138	(0.063, 0.168)	0.139
Acute cardiac disease (ACD)	0.128	(0.095, 0.155)	0.124
Other and unspecified NCD (uNCD)	0.099	(0.081, 0.129)	0.098
Acute respiratory infectious disease including pneumonia (ARI)	0.093	(0.055, 0.135)	0.094
Tuberculosis (TB)	**0.068**	**(0.051, 0.089)**	**0.064**
Other and unspecified cardiac disease (uCD)	0.045	(0.032, 0.067)	0.044
HIV/AIDS related death (HIV)	0.043	(0.026, 0.058)	0.024
Accident/fall	0.036	(0.036, 0.036)	0.036
Assault	0.033	(0.033, 0.03)	0.033
Other and unspecified neoplasms	0.027	(0.009, 0.047)	0.047

*The observed fraction is the proportion of cause-specific death observed in the sample and CSMF is the Bayesian estimate of the cause specific mortality fraction.
The focus of the article is mortality due to Tuberculosis, for that reason the cause specific death TB is highlighted.

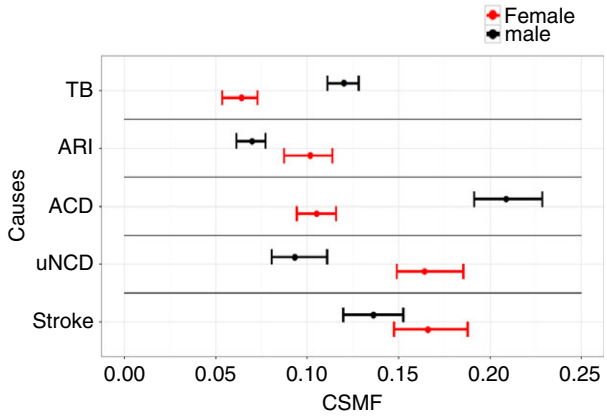

Figure 2 Top five cause specific mortality fractions by sex. [Colour figure can be viewed at wileyonlinelibrary.com].

Table 2 Fit of regression model of TBCSMF on age, sex, and area

Variable	Estimate	Standard error	*P*-value
Age			
50–65	−0.021	0.015	0.14
65+	−0.019	0.013	0.15
Sex			
Female	−0.043	0.010	0.0001*
Area			
Urban	0.013	0.012	0.27
Intercept	0.134	0.013	

*Indicates that the result is statistically significant which means *P* value is < 0.05.

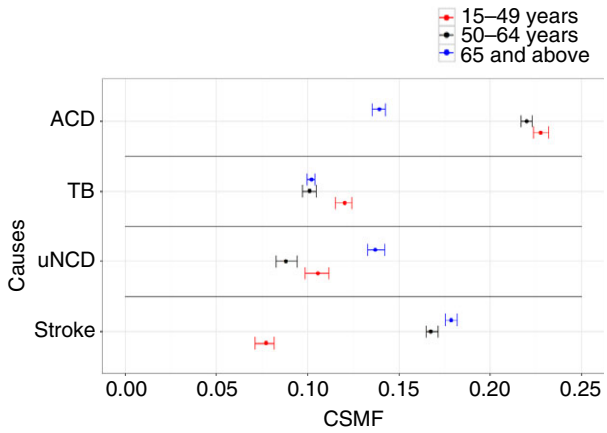

Figure 3 Top cause-specific mortality fractions by age group. [Colour figure can be viewed at wileyonlinelibrary.com].

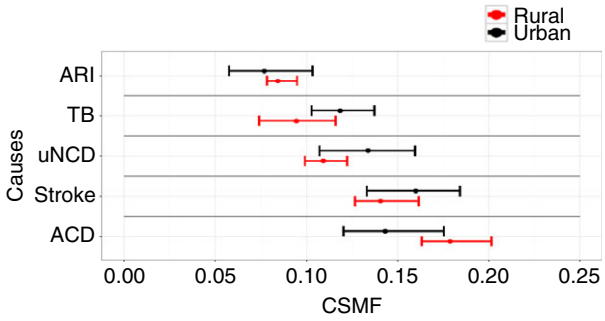

Figure 4 Top five cause specific mortality fractions by region (rural/urban). [Colour figure can be viewed at wileyonlinelibrary.com].

and 0.136 [95% CI: (0.091, 0.169), RO = 3] among males. Thus, the percentage of TB death among total deaths is much higher (female: 5.1%, male: 13.56%) among urban males than urban females.

Discussion

We found that TB is the fifth leading CoD in Bangladesh; generally, 6.8% of all deaths are related to TB. In 2006, based on estimates from the national TB program data and the sample registration systems, 8.5% of all deaths were due to by TB [25, 26] representing a 20% decline in the proportion of TB deaths among total deaths since 2006. The reduction is not statistically significant at 5% level of significance, but it could be significant at around 10% level. However, the evidence generally points to the fact that increased availability of free diagnostic and treatment services through DOTS program offered by NTP has greatly contributed to reduced TB mortality in Bangladesh. The result also mirrors the trend in TB prevalence from the recent survey, which was led by IEDCR and WHO, and exhibited a decline in the prevalence of TB by 22.78% over 10 years [5].

Globally, people aged 50 years and above carry the major TB burden [27]. It is important to note that in Bangladesh, although TB mortality is high among elderly (50+ years), being the second leading CoDs, TB also took a heavy toll among people aged 15–49 years. Nonetheless, TB was not among the leading CoDs for children of age less than 14 years, supported by the recent SVRS [26].

The most notable observation in our study was a sex differential in TB mortality; among males, 12% deaths are caused by TB, whereas 6.4% are among females. The sex difference in TB mortality, adjusted for age and region, was statistically significant.

TB is the third and fifth leading CoD among males and females, respectively. Both national and regional rates

show sex differential in the rate of TB death among total death. Both in rural and urban areas the difference in the percentages of TB death between males and females are high (rural: 4.0%, urban: 8.5%). However, the rate of TB death is highest among urban males (13.6%).

These results compare well with the sex difference among the registered TB patients from 2005 to 2013. The gap in death in those cohorts was profound (66–77% male) which can be explained by the bias observed in the enrolment to treatment (70–75% male patients) [16, 28]. A community-based active screening study also showed that prevalence in men is higher (62%) than in women (38%) with a ratio of 1.6:1 [29]. Another large door-to-door screening in 74 *Upazila* also showed that more men were diagnosed with TB than women and that it is not related to the inaccessibility of women [30].

Therefore, it is evident that the resulting disease incidence is thus primarily a direct consequence of the underlying prevalence of latent infection. The dispartity in death is further supported by the findings from a treatment outcome study where more female than male patients who underwent treatment achieved cure (93% *vs*. 89%) [31]. Given the very low HIV prevalence, the reasons for higher mortality among men could be due to older age, more co-morbidities, and worse treatment outcomes [31].

Generally, urban areas are more polluted and crowded than rural areas. In Bangladesh, smoking and exposure to crowds is more common among men than women. These factors may contribute to sex and regional differences in rate of TB death among total death. Further study on risk behaviours of both men and women in urban and rural areas might reveal the underlying reasons for the sex and regional gap. Urban areas remain a place for higher mortality rate due to TB (11.9%) than rural areas (9.4%). The respective proportions were 10.7% and 7.8% in 2006 [26]. The regional difference in TB death could be explained by the higher prevalence in urban areas. A survey in 2015 found that TB prevalence was higher among the urban (334/100 000) than the rural 274/100 000 population [5]. This is corroborated by a recent community-based active screening study in an urban slum where the prevalence was 400/100 000 population [29]. Urban areas in Bangladesh are densely populated, and about one-third of the population are slum dwellers, creating conditions for high transmission of tuberculosis.

We used the 2012 InsilicoVA method [19,20], as data-driven models are fast, low-cost, and reliable, and increasingly preferred over physician review for analysing VA data to determine CoD [21, 22]. The conventional data-driven methods, e.g., InterVA, provide the assigned probability of a CoD only, but fail to provide a measure of uncertainty. InsilicoVA overcomes this limitation to provide overall population cause specific mortality fraction (CSMF) (the proportion of death caused by a specific disease) and individual level CSMF with associated credible interval. Moreover, it incorporates the variability in individual CoD, i.e., whether the probability that a person died from a specific cause is high or low, in calculating CSMF. In 2016, WHO launched a new version of Insilico VA that fully incorporates the indicators necessary to run currently available automated diagnostic algorithms [32].

There were some limitations, such as the local death register of BBS not always being up to date, and a few PSUs being very hard to reach. Besides, VA is a complicated tool which itself is subject to recall bias. Nonetheless, BBS results have been criticised for using a layman system, and the findings of our study shows that SVRS results are comparable. We recommend BBS may administer standard VA to overcome the limitations of SVRS.

Accurate measurement of TB mortality in Bangladesh is required to assess the scale of the problem. This research will help the NTP in policy-making for TB prevention and control in Bangladesh. Our findings suggest that future research should explore the underlying reasons for the higher rate of TB-related death in urban areas and among male patients with TB.

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